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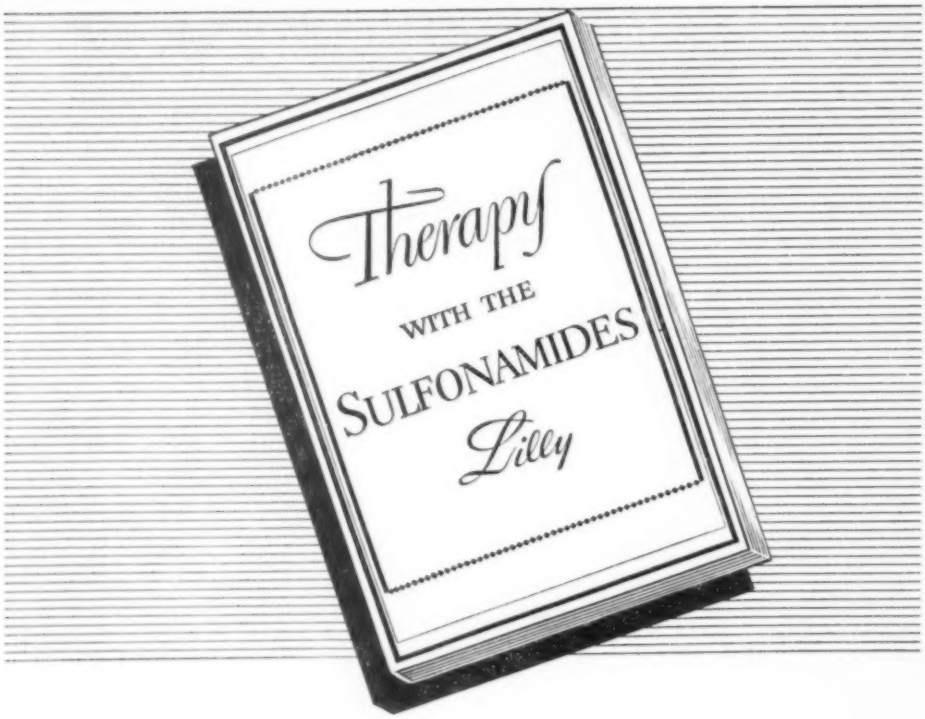
TABLE OF CONTENTS ON 3rd COVER



Therapy with the Sulfonamides

In 1937 sulfanilamide was introduced into general clinical use. During the next six years sulfapyridine, sulfathiazole, sulfadiazine, and sulfamerazine followed in rapid succession. The vast clinical literature which has accumulated in the interval has been carefully organized and condensed by the Lilly Research Laboratories into an eighty-three-page book entitled *Therapy with the Sulfonamides*. A bibliography of 323 references is included. The discussion is divided between systemic and local administration. Many helpful charts, including "Sulfonamides in Order of Choice for Systemic Use," "Dosage of Sulfonamides for Adults," and "Dosage of Sulfonamides for Infants and Children," are included. Request a free copy of *Therapy with the Sulfonamides* from the Lilly medical service representative or direct from Indianapolis. Sulfonamides, Lilly, for systemic and local administration are provided in a complete variety of dosage forms, subject to your specifications.

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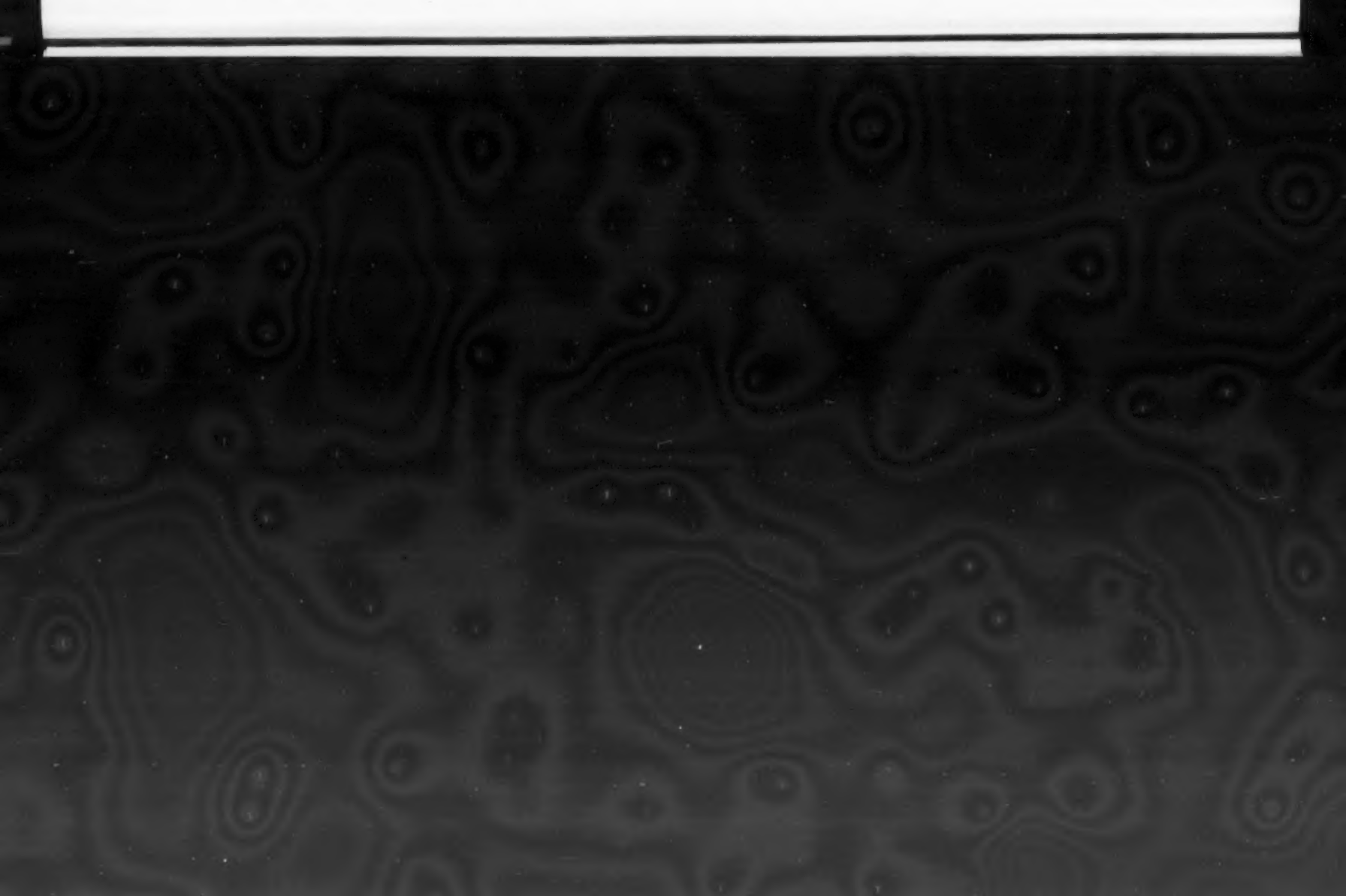

The Journal of Pediatrics

VOL. 29 OCTOBER, 1946 NO. 4

Original Communications

HISTOPLASMIN SENSITIVITY

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IN TWO previously reported studies[1, 2] on the problems associated with the finding of pulmonary calcification in people insensitive to tuberculin, we were able to show that there is a remarkable correlation between histoplasmin sensitivity and calcified nodules in the lungs. This relationship was also reported by Palmer,[3] and his subsequent studies[4] have tended to elaborate and confirm this relationship. From our studies we thought that considerable significance could be attached to the age relationships in the development of sensitivity to tuberculin and histoplasmin and the age at which calcium deposits begin to appear in the chests of the children studied.

The early studies on the epidemiology of the unexplained calcifications, the data accumulating from our skin testing program, studies by Smith,[5] the studies of Palmer[3, 4] and his associates, and the observations of the Williamson County Tuberculosis Study[6] have indicated considerable geographic variation in the prevalence of unexplained pulmonary calcifications and sensitivity to histoplasmin.

These studies have, of course, raised the question of how much significance can be attached to the finding of histoplasmin sensitivity.

Our experience, which now exceeds 2,000 histoplasmin tests in various age groups and from a considerable area of the country, is sufficient to enable us to add pertinent observations concerning the features of histoplasmin sensitivity.

STUDY MATERIAL

The children and young adults whom we have examined have been drawn from three groups:

Group I. A. 181 children, aged 2 to 19 years, from a child-caring institution in Williamson County, Tenn., the children chiefly originating from Middle Tennessee* and

From the Department of Pediatrics, Vanderbilt University School of Medicine.
Presented before the Meeting of the American Pediatric Society, Skytop, Pa., May 2, 1946.
*Reported in detail.[1]

B. 315 children, aged 6 to 19 years, residents of the Tennessee Industrial School and having primary residence scattered over the whole of Tennessee.*

Group II. 1,255 students at Vanderbilt University
A. 611 of whom were from Tennessee and
B. 644 from outside Tennessee

Group III. 381 patients tested at Vanderbilt University Hospital as in-patients and outpatients, chiefly residents of Middle Tennessee.

Groups I and II have been examined by chest roentgenograms, stereoscopic 4 by 5 inch films. Some of the children in Group III have had chest size, 7 foot, single films. All have been tested to histoplasmin† 0.001 c.c. and to 0.01 mg. or more of old tuberculin.

Individuals from Groups I and III were, in general, from the lower economic strata of their communities; Group II, on the other hand, was composed of college students and is more representative of the other economic extreme.

We have in these groups 1,488 children and young adults from Tennessee. In this group the age relationships of the phenomena of tuberculin sensitivity and histoplasmin sensitivity can be compared. As all children at Vanderbilt Hospital are not examined by x-ray, this group is excluded in the tabulations of pulmonary calcification. This leaves a group of 1,107 in which the age of the finding of pulmonary calcification by chest roentgenogram can be contrasted to the age relationship of tuberculin and histoplasmin sensitivity.

The Concurrence of Histoplasmin Sensitivity and Pulmonary Calcifications.—It is of interest at this point to diverge from our main thesis and to re-examine our over-all findings concerning the concurrence of histoplasmin sensitivity and pulmonary calcification. In Table I is shown the observed relationships between histoplasmin sensitivity and pulmonary calcification, and between the latter and tuberculin sensitivity.

TABLE I. NUMBER AND PER CENT SHOWING PULMONARY CALCIFICATIONS ACCORDING TO REACTIONS TO HISTOPLASMIN AND TUBERCULIN BY GROUPS

	RESIDENTS OF TENNESSEE									NONRESIDENTS		
	TOTAL			GROUP I			GROUP IIA			GROUP IIB		
		WITH CALCIUM			WITH CALCIUM			WITH CALCIUM			WITH CALCIUM	
REACTION	TOTAL	NO.	%	TOTAL	NO.	%	TOTAL	NO.	%	TOTAL	NO.	%
TOTAL	1,107	610	55.1	496	253	51.0	611	357	58.4	644	240	37.3
Histoplasmin + Tuberculin +	168	99	58.9	91	58	63.7	77	41	53.2	34	23	67.6
Histoplasmin + Tuberculin −	701	434	61.9	273	161	59.0	428	273	63.8	181	93	51.4
Histoplasmin − Tuberculin +	38	16	42.1	21	9	42.8	17	7	41.2	70	28	40.0
Histoplasmin − Tuberculin −	200	61	30.5	111	25	22.5	89	36	40.4	359	96	26.7

*Reported in detail.[2]

†A positive reaction is 5 mm. or more of induration and redness resulting from the intradermal injection of 0.001 ml. of filtrate of a broth culture of *Histoplasma capsulatum*. See Reference.[1]

In Table I, Group II has been subdivided into two classes, those residing within Tennessee and those whose primary residence is outside of the State. The total is for Tennessee residents and excludes those living outside of the State. Sixty-two per cent of the Tennessee residents who are sensitive to histoplasmin but not to tuberculin show pulmonary calcification, while only 42 per cent of those tuberculin-sensitive and histoplasmin-insensitive show pulmonary calcifications. A similar trend in difference is noted among the nonresidents of Tennessee who show 40 per cent calcifications among the tuberculin-sensitive histoplasmin-insensitive, and 51.4 per cent calcifications among the histoplasmin-sensitive tuberculin-insensitive individuals.

In Table II we have broken down the data on the skin reactions of the 610 individuals from Tennessee who showed pulmonary calcifications. It is apparent from this table that 87.4 per cent of those having pulmonary calcifications are sensitive to histoplasmin while only 18.8 per cent are tuberculin-sensitive.

TABLE II. HISTOPLASMIN AND TUBERCULIN REACTIONS IN 610 INDIVIDUALS FROM TENNESSEE HAVING PULMONARY CALCIFICATIONS

	NUMBER		PER CENT OF ALL INDIVIDUALS WITH CALCIFICATION	
Histoplasmin + Tuberculin +	99*		16.2	
Histoplasmin + Tuberculin −	434		71.1	
Subtotal Histoplasmin +		533		87.4
Tuberculin + Histoplasmin +	99*		16.2	
Tuberculin + Histoplasmin −	16		2.6	
Subtotal Tuberculin +		115		18.8
Histoplasmin − Tuberculin −		61		10.0

*These individuals are duplicated to make subtotals correct.

In conjunction with the over-all correlation of histoplasmin sensitivity and pulmonary calcification, it is of interest to examine our data for the relationship to sensitivity and the degree of calcification. In Table III we have shown pulmonary calcifications divided into marked, i.e., multiple peripheral and hilar calcifications; moderate, i.e., single hilar and peripheral calcifications; and minimal, i.e., single hilar or peripheral lesions, both questionable and indubitable.

TABLE III. THE RELATIONSHIP OF THE DEGREE OF PULMONARY CALCIFICATION TO HISTOPLASMIN AND TUBERCULIN SENSITIVITY

TYPE OF SKIN REACTION	DEGREE OF CALCIFICATION								ALL WITH CALCIFICATION		TOTAL	
	MARKED		MODERATE		MINIMAL		NONE					
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Histoplasmin positive	96	86.1	419	79.8	135	62.2	434	48.2	650	76.4	1,084	61.9
Tuberculin positive	23	21.1	104	19.8	39	18.0	144	16.0	166	19.5	310	17.7
Histoplasmin and tuberculin negative	9	8.2	80	15.2	68	31.3	402	44.7	157	18.4	559	31.9
Total*	109		525		217		900		851		1,751	

*As some individuals react to both antigens, the columns do not add up to the indicated totals.

Eighty-eight per cent of those with marked pulmonary calcifications were sensitive to histoplasmin; 62 per cent in the minimal calcification group were sensitive; and 48 per cent who showed no calcifications were positive. In the

tuberculin-sensitive group the corresponding percentages are 21, 18, and 16. It is also interesting to note that while only 9 of 109 with marked calcifications and 80 of 525 with moderate calcifications were insensitive to both histoplasmin and tuberculin, 402 of 900 who did not have calcifications failed to react to either antigen. This, of course, includes those too young to have developed calcifications and those who may have had calcifications and resolved them.

These findings confirm and elaborate the previous reports concerning the relationship of histoplasmin sensitivity to pulmonary calcifications.

Age Distribution.—In Table IV is shown the age distribution and the results of the histoplasmin tests in the various groups. In this table it is interesting to note that while only one child of 52 (1.9 per cent) reacted to histoplasmin the first year, in the second and third years there were 15 of 82 (18.3 per cent) who had developed sensitivity to the antigen. In the third and fourth years this rapid development of sensitization continues—23 of 63 (36.0 per cent) have become sensitized. The prevalence of sensitization then gradually increases with increased age until a maximum of 90 per cent is reached in the 21 through 22 year group.

TABLE IV. THE NUMBER TESTED AND PER CENT SHOWING POSITIVE REACTIONS TO HISTOPLASMIN BY AGE IN STUDY GROUPS

AGE	NUMBER TESTED				PER CENT POSITIVE			
	GROUP I	GROUP II	GROUP III	TOTAL	GROUP I	GROUP II	GROUP III	TOTAL
Under 1 year	0	0	52	52	–	–	1.9	1.9
1- 2	2	0	80	82	0.0	–	18.7	18.3
3- 4	10	0	53	63	50.0	–	24.0	36.5
5- 6	18	0	53	71	50.0	–	34.0	38.0
7- 8	35	0	38	73	65.7	–	42.1	53.4
9-10	52	0	40	92	65.4	–	52.5	59.8
11-12	108	0	37	145	75.9	–	56.8	64.1
13-14	130	0	29	159	76.1	–	65.5	74.2
15-16	101	8	0	109	86.1	75.0	–	85.3
17-18	35	214	0	249	85.7	79.9	–	80.7
19-20	4	182	0	186	100.0	85.2	–	85.5
21-22	1	93	0	93	100.0	90.2	–	90.3
23-24	0	42	0	42	–	76.2	–	76.2
25-29	0	28	0	28	–	82.1	–	82.1
30 or more	0	45	0	45	–	77.8	–	77.8

Table V shows the results of tuberculin testing by age in the various groups.

The development of tuberculin sensitivity in these groups follows a quite different pattern from that observed concerning histoplasmin sensitivity. None of 52 children under 1 year of age were sensitive but in the group 1 through 2 years of age there were 5 of 82 (6.1 per cent) positive. There was then a slow increase in the prevalence of sensitization in the low economic class represented by Group I until a maximum of 15 of 35 (42.8 per cent) was reached in the age group 17 through 18 years. At this point the classes shift and young adults from the high economic plane represented by the university students become the greatly predominant group. It is interesting to note that in this group for the same age, 17 through 18 years, only 27 of 214 (12.6 per cent) are tuberculin-sensitive.

TABLE V. NUMBER TESTED AND PER CENT SHOWING POSITIVE REACTIONS TO TUBERCULIN BY AGE AND BY GROUP

AGE	NUMBER TESTED				PER CENT POSITIVE			
	GROUP I	GROUP II	GROUP III	TOTAL	GROUP I	GROUP II	GROUP III	TOTAL
Under 1 year	0	0	52	52	–	–	0.0	0.0
1-2	2	0	80	82	0.0	–	6.2	6.1
3-4	10	0	53	63	0.0	–	3.8	3.2
5-6	18	0	53	71	11.1	–	11.3	11.3
7-8	35	0	38	73	17.1	–	10.5	13.7
9-10	52	0	40	92	3.8	–	25.0	13.0
11-12	108	0	37	145	23.1	–	18.9	22.0
13-14	130	0	29	159	23.8	–	27.6	24.5
15-16	101	8	0	109	30.7	0.0	–	28.4
17-18	35	214	0	249	42.8	12.6	–	16.8*
19-20	4	182	0	186	0.0	13.2	–	12.9
21-22	1	93	0	93	0.0	17.4	–	17.2
23-24	0	42	0	42	–	19.0	–	19.0
25-29	0	28	0	28	–	25.0	–	25.0
30 or more	0	45	0	45	–	26.7	–	26.7

*At this point the group balance shifts from the low economic levels represented by Groups I and III to the high economic level represented by Group II, college students.

In Table VI is shown the development of pulmonary calcification by age in Groups I and II.

The development of pulmonary calcification, while not observed in the children less than 5 years of age, increased very sharply from this period to attain a level of 57.7 in the group 9 through 10 years. From this period on the acquisition of pulmonary calcification is very gradual, reaching a maximum level of 66.7 per cent in the 19 through 20-year group, and with a tendency to fall off in the older age groups.

TABLE VI. THE NUMBER X-RAYED AND PER CENT SHOWING CALCIFICATIONS BY AGE IN GROUPS I AND II

AGE	NUMBER X-RAYED			PER CENT WITH CALCIFICATION		
	GROUP I	GROUP II	TOTAL	GROUP I	GROUP II	TOTAL
Under 1 year	0	0	0	–	–	–
1-2	0	0	2	0.0	–	0.0
3-4	10	0	10	0.0	–	0.0*
5-6	18	0	18	16.7	–	16.7
7-8	35	0	35	42.8	–	42.8
9-10	52	0	52	57.7	–	57.7
11-12	108	0	108	50.0	–	50.0
13-14	130	0	130	58.5	–	58.5
15-16	101	8	109	51.2	75.0	53.2
17-18	35	214	249	51.4	59.8	58.6
19-20	4	182	186	100.0	65.9	66.7
21-22	1	92	93	100.0	44.6	45.2
23-24	0	42	42	–	50.0	50.0
25-29	0	28	28	–	71.4	71.4
30 or more	0	45	45	–	46.7	46.7

*Though not tabulated because of incomplete observations, roentgenograms of Group III also show absence of calcification in the youngest age groups.

The relationships of these observations can be more easily seen in graphic representation. In Chart 1 are shown the curves for the development of pulmonary calcification, tuberculin sensitivity, and histoplasmin sensitivity for all

groups except in the calcification curves where Group III is omitted because of incomplete observation.

This Chart brings out strikingly the fact that in the 17 through 18-year group the prevalence of tuberculosis as measured by tuberculin tests is three times as high in children from the lower economic group as contrasted to university students.

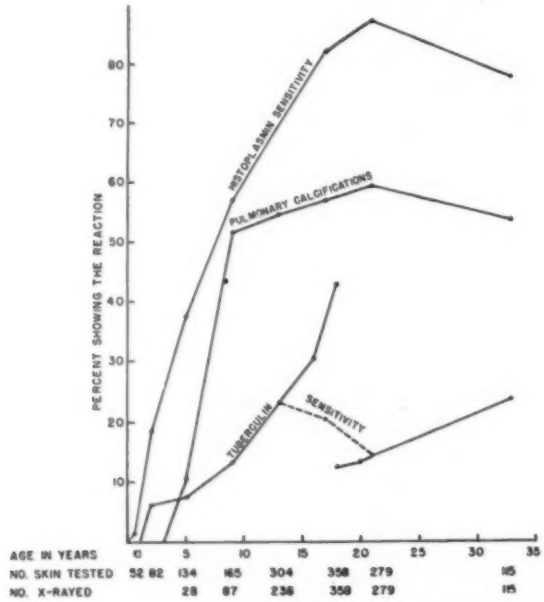

Chart 1.—Age relationship in the development of histoplasmin sensitivity, pulmonary calcification, and tuberculin sensitivity.

More pertinent to this study is the relationship of the curves for the development of histoplasmin sensitivity and pulmonary calcification. Here it is apparent that while there is a considerable lag in the development of pulmonary calcification as compared with histoplasmin sensitivity their relationship is such that the pulmonary calcification could follow and be related to the development of the histoplasmin sensitivity. This is of greater significance in view of the findings in our previous studies and those of Palmer[3] which show a high degree of correlation between the presence of histoplasmin sensitivity and pulmonary calcification.

It is also of interest to note that while there is a coincidence of the peak of histoplasmin sensitivity and pulmonary calcification, the same is not true for tuberculin sensitivity. It is also of considerable significance that the peak and depression of tuberculin sensitivity found by superimposing the groups of differing economic status is in no way reflected in the curve of pulmonary calcification. This in itself seems to indicate that there is a more intimate relationship

between the presence of histoplasmin sensitivity and pulmonary calcification than between this latter phenomenon and tuberculin sensitivity, at least in the groups observed.

Another point of interest concerning the relationship of these observations is the fact that early pulmonary calcification follows histoplasmin sensitivity more intimately than is the case in the ages beyond puberty. This point will be subjected to analysis later.

Geographical Distribution.—The examination of the geographical pattern of sensitivity distribution and pulmonary calcification is of interest not only because it gives some indication of the relative presence or absence of infection in a given area, but also because the fluctuations in different areas aid in examining the relationship of the phenomena, and finally because the variations are of value in assessing the significance of the histoplasmin test.

Among the children and young adults of Groups I and II we have 926 persons from the State of Tennessee and 644 from outside the State but principally from states in the southeastern section of the United States and from Pennsylvania, New Jersey, and New York.

In Table VII is shown the distribution of histoplasmin and tuberculin sensitivity and pulmonary calcifications of Groups I and IIA, aged 2 through 30 years, by six arbitrary divisions of the State of Tennessee. In some divisions the numbers are not large but in all they are enough to indicate the general pattern of the reactions. In this table it is readily apparent that pulmonary calcifications vary in each segment directly with the histoplasmin sensitivity. The eastern sections of the State with low prevalence of histoplasmin sensitivity also show the lowest prevalence of pulmonary calcifications. On the other hand the East East section with the lowest incidence of pulmonary calcifications was in tuberculin sensitivity next to the East West segment where the highest prevalence of both tuberculin sensitivity and pulmonary calcifications was observed. Also, there is in every section much more calcification than can be explained on the basis of tuberculous infections as indicated by the tuberculin test. In general, there was a less direct relationship between the relative levels of tuberculin sensitivity and pulmonary calcifications than between the latter and histoplasmin sensitivity.

TABLE VII. NUMBER AND PER CENT OF PERSONS FROM TENNESSEE SHOWING PULMONARY CALCIFICATIONS, HISTOPLASMIN SENSITIVITY AND TUBERCULIN SENSITIVITY ACCORDING TO THEIR RESIDENCE IN SIX SECTIONS OF THE STATE

SECTIONS OF TENNESSEE	TOTAL	HISTOPLASMIN		CALCIFICATION		TUBERCULIN	
		NO. POS.	% POS.	NO. POS.	% POS.	NO. POS.	% POS.
TOTAL	926	737	79.6	531	57.3	161	17.4
East East	74	31	41.9	20	27.0	16	21.6
West East	50	25	50.0	16	32.0	5	10.0
East Middle	41	32	78.0	19	46.3	7	17.1
West Middle	626	536	85.6	389	62.1	105	16.8
East West	33	27	81.8	23	69.7	9	27.3
West West	101	86	85.1	63	62.4	19	18.8
Unknown	1			1			

In Charts 2 and 3 are shown the sectional distribution for Tennessee of histoplasmin sensitivity and pulmonary calcifications, respectively. Here it is graphically demonstrated that there is a close association between histoplasmin sensitivity and pulmonary calcification.

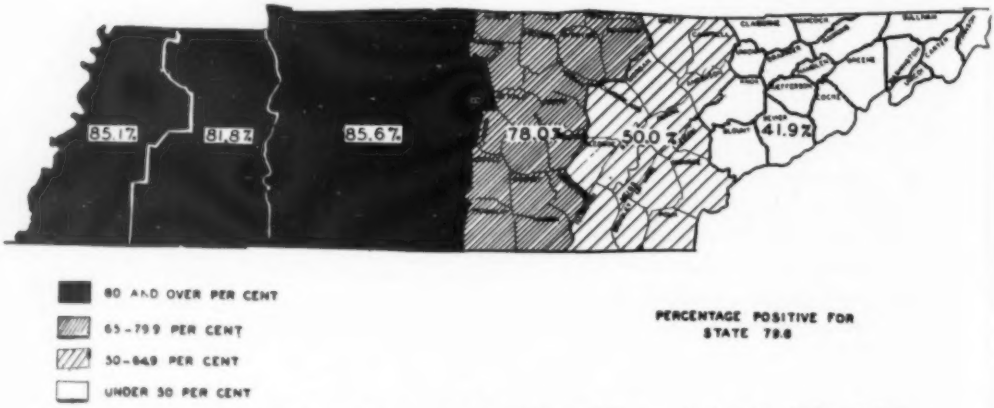

Chart 2.—Percentage of persons (by county of residence, 1945) examined at Vanderbilt University and Tennessee Industrial School who reacted to histoplasmin.

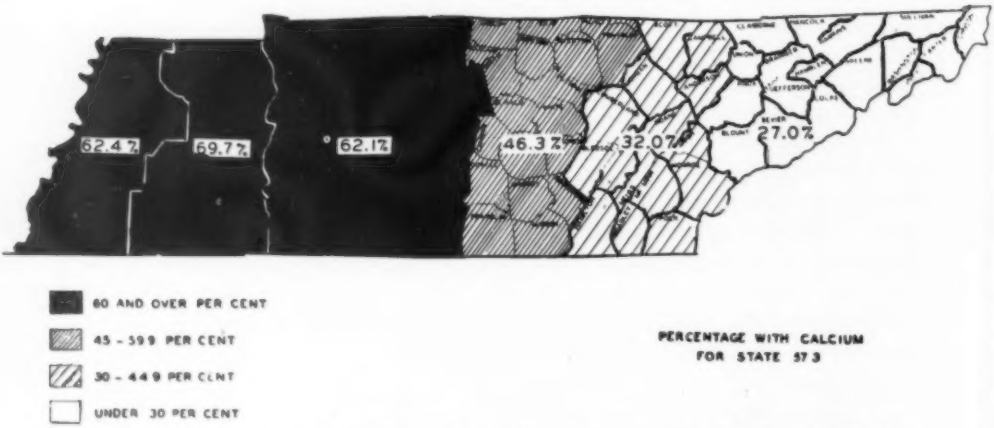

Chart 3.—Percentage of persons (by county of residence, 1945) examined at Vanderbilt University and Tennessee Industrial School who were found to have calcification.

In Table VIII and Charts 4 and 5 is shown the geographical distribution of sensitivity to histoplasmin and tuberculin and of pulmonary calcifications in the people of Group II. Group I is omitted because it does not represent a comparable age group.

The fact that most of the people come from states adjacent to Tennessee which are areas with a high incidence of histoplasmin sensitivity makes the

TABLE VIII. NUMBER AND PER CENT OF PERSONS AT VANDERBILT UNIVERSITY HAVING PULMONARY CALCIFICATIONS, HISTOPLASMIN SENSITIVITY AND TUBERCULIN SENSITIVITY ACCORDING TO STATE OF PRIMARY RESIDENCE

STATE	TOTAL	HISTOPLASMIN-POSITIVE		CALCIFICATION ON X-RAY		TUBERCULIN-POSITIVE	
		NO.	%	NO.	%	NO.	%
TOTAL	1255	720	57.4	597	47.6	198	15.8
Alabama	77	36	46.8	27	35.1	12	15.6
Arizona	1	0	–	0	–	0	–
Arkansas	19	9	47.4	7	36.8	2	10.5
California	5	1	*	0	–	1	*
Colorado	1	0	–	0	–	1	*
Connecticut	4	3	*	0	–	0	–
District of Columbia	2	0	–	1	*	0	–
Florida	30	6	20.0	10	33.3	3	10.0
Georgia	43	5	11.6	11	25.6	0	–
Illinois	13	3	23.1	6	46.2	1	7.7
Indiana	11	6	54.5	4	36.4	4	36.4
Iowa	1	0	–	0	–	0	–
Kansas	2	1	*	0	–	0	–
Kentucky	56	47	83.9	36	64.3	13	23.2
Louisiana	11	4	36.4	6	54.5	0	–
Maryland	3	1	*	1	*	0	–
Massachusetts	2	0	–	0	–	0	–
Michigan	6	1	*	3	*	1	*
Minnesota	1	0	–	0	–	0	–
Mississippi	32	19	59.4	18	56.2	3	9.4
Missouri	11	8	72.7	7	63.6	4	36.4
New Hampshire	1	0	–	0	–	0	–
New Jersey	61	5	8.2	19	31.1	17	27.9
New Mexico	1	0	–	0	–	0	–
New York	76	8	10.5	21	27.6	13	17.1
North Carolina	12	4	33.3	4	33.3	3	25.0
Ohio	9	5	*	7	*	0	–
Oklahoma	9	4	*	3	*	1	*
Oregon	1	1	*	1	*	0	–
Pennsylvania	39	8	20.5	14	35.9	8	23.1
South Carolina	27	4	14.8	4	14.8	4	14.8
Tennessee	611	505	82.6	357	58.4	94	15.4
Texas	27	7	25.9	4	14.8	4	14.8
Virginia	15	5	32.3	6	40.0	1	6.7
Washington	1	0	–	1	*	0	–
West Virginia	14	3	21.4	6	42.9	3	21.4
Wisconsin	2	0	–	1	*	1	*
Wyoming	1	0	–	0	–	0	–
Out of country	4	2	*	1	*	2	*
Unknown	13	9	69.2	11	84.6	1	–

*Percentages not calculated for states with less than ten examined.

over-all histoplasmin sensitivity high. In general, it may be seen that the percentage of histoplasmin reactors is higher in the states of the Western Appalachian slope and those just west of the Mississippi River. The states having the highest prevalence of histoplasmin sensitivity have, in general, the highest incidence of pulmonary calcifications. The numbers of individuals tested in the states outside of Tennessee are usually so low that little more than tendencies can be shown.

The relationship of pulmonary calcifications to tuberculin sensitivity is not as regularly apparent.

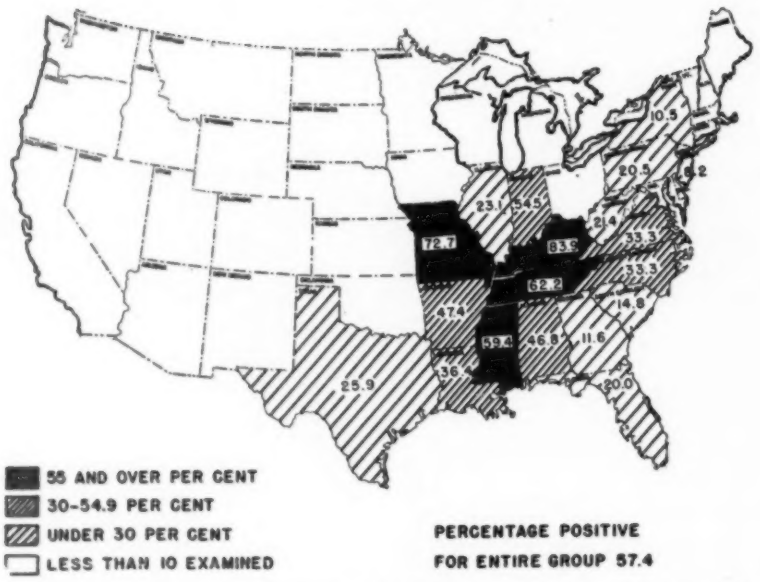

Chart 4.—Distribution by state of residence of the percentage of persons who were examined at Vanderbilt University in 1945, and found to react to histoplasmin.

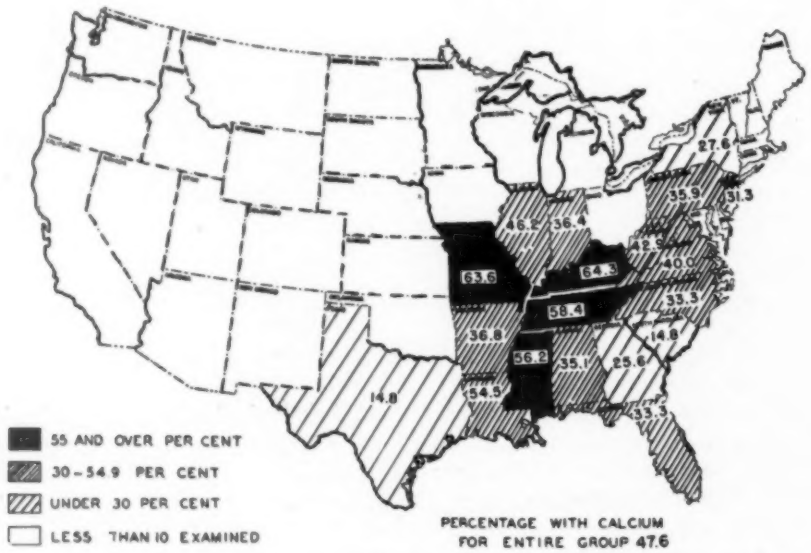

Chart 5.—Distribution by state of residence of the percentage of persons who were examined at Vanderbilt University in 1945, and found to have calcification.

In Table IX we have set up two groups for contrast. Students from states other than Tennessee* with more than 10 individuals having less than 25 per cent sensitivity to histoplasmin are contrasted with those† having more than 25 per cent histoplasmin sensitivity. The sensitivity to tuberculin and histoplasmin and the calcification by degrees of calcification as well as the total are shown. From this table it may be seen that while there is a 65 per cent higher incidence of tuberculin sensitivity among the students from the states of low histoplasmin sensitivity, there is among these students only 65 per cent as much pulmonary calcification as in the states with high histoplasmin sensitivity. Furthermore, the pulmonary calcifications in those students from low histoplasmin-sensitivity areas are 48 per cent of the minimal degree and only 2 per cent of the marked degree, while those from high histoplasmin-sensitivity areas show only 22 per cent minimal calcifications, 65 per cent moderate calcifications, and 13 per cent marked calcifications.

TABLE IX. THE CONTRAST OF TUBERCULIN SENSITIVITY, HISTOPLASMIN SENSITIVITY AND PULMONARY CALCIFICATIONS IN GROUPS OF STATES HAVING LOW AND HIGH PREVALENCE OF HISTOPLASMIN SENSITIVITY

	NUMBER OF INDIVIDUALS	CALCIFICATION								HISTOPLASMIN POSITIVE		TUBERCULIN POSITIVE	
		TOTAL		DEGREE									
				1		2		3					
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
States with low prevalence of histoplasmin sensitivity*	303	91	30.0	44	48.3	45	49.4	2	2.2	45	14.8	50	16.5
States with high prevalence of histoplasmin sensitivity†	262	119	45.4	26	21.8	77	64.7	16	13.4	82	31.3	26	9.9

*Florida, Georgia, Illinois, New Jersey, New York, Pennsylvania, South Carolina, West Virginia.

†Alabama, Arkansas, Indiana, Kentucky, Louisiana, Mississippi, Missouri, North Carolina, Texas, Virginia.

The Significance of Histoplasmin Sensitivity.—From the studies to date it is apparent that a positive histoplasmin test even in fairly young individuals cannot have great significance as an indicator of active disease. In children, 4 through 5 years old, 50 per cent have become sensitized and are without any evidence of a clinically significant infection. The value it might have as an exclusion test is clouded because most of the patients with advanced proved histoplasmosis who have been tested have been found negative. Parsons and Zarafonetis,[7] Davis and Neff,[8] and McLeod, Emmons, Ross, and Burke,[9] have reported patients with miliary histoplasmosis who failed to react to histoplasmin. We are also acquainted with another case in a patient of Crosswell[10] who failed to react to histoplasmin. While the failure may have been due to the use of inadequate dilutions of outdated antigen in the case of Parsons and Zarafonetis, as they suggested, the same is not true in the other cases where known potent histoplasmin was used. Our interest in the test resulted in part from a positive

*Florida, Georgia, Illinois, New Jersey, New York, Pennsylvania, South Carolina, West Virginia.

†Alabama, Arkansas, Indiana, Kentucky, Louisiana, Mississippi, Missouri, North Carolina, Texas, and Virginia.

response obtained in a 5-month-old infant who was dying with histoplasma sepsis, an instance where one might have expected to have found an exhaustion anergy. It is of some interest to note that all the parents of the last five patients mentioned reacted strongly to histoplasmin. It is probable that the test, like the tuberculin test, is satisfactory as an exclusion test in the mild acute, subacute, and chronic forms of the infection. It would seem quite probable that less sensitivity might exist during a time when the infection is very active, comparable to the anergy seen in tuberculin testing during miliary infections. It is suggested under such circumstances that tests with a series of dilutions be used, through to the 1:10 dilution with presently available preparations.

The recent studies of Emmons, Olson, and Ethridge[11] have cast considerable doubt upon the specificity of the histoplasmin test. They have shown that histoplasmin reacts almost invariably in animals experimentally infected with *Blastomyces dermatitidis* or *Haplosporangium parvum* and much less frequently in experimental infections with *Coccidioides immitis*. On the other hand, blastomycin and coccidioidin reacted much less commonly in a nonspecific manner; the blastomycin reacted with only 17 of 39 animals infected with *H. capsulatum*, with none of 7 infected with *C. immitis* and with 6 of 7 infected with *Haplosporangium parvum*.

From these observations one might say that histoplasmin gave frequent nonspecific reactions; that it may well serve as an index of sensitization to various fungi. It has been stated in previous studies[1, 2, 3] that such a situation might exist; that the histoplasmin sensitivity may be indicative of more than *H. capsulatum* infection; that it might be indicative of sensitization by some agent having an antigenic complex closely related to that of histoplasmin.

In one of our studies[1] we have reported on the responses of 125 children and young adults of Tennessee to coccidioidin. While there were many in the group who reacted to histoplasmin, there was not one who gave a clear-cut positive reaction to coccidioidin. Similarly in another group tested to histoplasmin[2] we carried out simultaneous skin tests with haplosporangin. In the group of over 300 so tested there were only two doubtful reactions, none acceptably positive.

As far as these findings go they were in general agreement with those of Emmons[11] as his study showed haplosporangin reacting very specifically and coccidioidin reacting only once in 39 animals infected with *H. capsulatum*, once in 8 animals infected with *B. dermatitidis*, and in 4 of 7 animals infected with *Haplosporangium parvum*. It would seem, however, that there is less tendency for cross-reactions to occur in children and young adults than in experimental animals as judged by the failure to get any false reactions with coccidioidin.

The failure to find many young infants sensitive to histoplasmin would make it seem very unlikely that infection with *Candida albicans* can be of real significance in relationship to histoplasmin sensitivity. Oral thrush is a common infection of infants in this section and would, if it produced cross-sensitivity reactions, be likely to yield a high percentage of infantile reactors. Furthermore, thrush is not a commonly recognized infection among the children of the age groups where we commonly see histoplasmin sensitivity.

There is certainly need for further study, in groups such as we have studied, of sensitization to the antigens derived from other fungi responsible for systemic mycoses. The study of Emmons[11] showed that there was a marked mutual crossing of the reactions to histoplasmin and blastomycin in experimentally infected animals and in patients with chronic pulmonary disease. This would clearly indicate a need for further study of the cross-reactions of these antigens and also the need to examine clinical material for the possibility of unrecognized mild forms of blastomycosis.

Our studies yield information which makes it seem quite certain that the reactions observed are truly allergic phenomena, reactions to some antecedant infection, rather than being simple reactions to nonspecific irritants contained in the preparation.

In regard to this, the pattern of age response is such as one would expect from a widely disseminated infectious agent. Sensitization occurs only very rarely in early infancy. The only positive reaction we have encountered in a child less than 6 months of age was in an infant dying with proved histoplasmosis and we have seen only one other positive reaction in an infant less than 1 year of age. The rapid increase in sensitization in the next few years of life is certainly not correlated with any particular developmental achievement. It is rather like the development of Schick negativeness in the nonimmunized urban groups, a phenomenon no longer generally believed to be due to normal development but generally attributed to immunizations resulting from subclinical infections, the clinical horizon for which might be lowered by improvement in clinical perception or the development and wider use of improved laboratory techniques in demonstrating the infection.

The character of the responses obtained might be cited; in the young the reactions tend to be ++ and +++ in a high proportion of the cases, while in older age groups + reactions are more frequent. This may be interpreted as suggesting that the reaction is more vigorous when first developed but tends to become attenuated after a time, even where reinfection occurs to maintain the reaction. A similar phenomenon is observed in tuberculous infection where "epituberculosis" or massive benign perifocal allergic reaction with its extreme sensitization, generally as well as locally, is a pecularity of early childhood infection.

The geographical distributions of histoplasmin sensitivity also offer strong support for the supposition that the reaction is a response to an infectious process. Our studies showing the geographical pattern of sensitivity to histoplasmin are unfortunately, to date, entirely in the older children and young adults.

These studies, however, show that there is a wide variation in the incidence of sensitivity from one area to another within the State of Tennessee. Indeed, the extensive studies reported by Palmer[4] showed that there was in other states a similar variability and that this variability in states bordering the areas of high prevalence of sensitivity was integrated with the geographical relationship of the state to the bordering areas of high prevalence of

sensitivity. If we assume, as seems apparent, that the center of this infection is in Kentucky and Missouri, our findings in the State of Tennessee show a similar gradation.

Furthermore, the wide variation in sensitivity observed in our studies in students from different states, and in the studies of Palmer[3, 4] shows that the variation is in relationship to a fairly definite geographical focus and is suggestive of an infectious agent existing commonly in an area where climatic factors favor its propagation. A similar relationship has been recognized in the problem of coccidioidomycosis, an infection in which sharply delimited foci of propagation and infection have been demonstrated.

In California, Smith[5] has observed that there is almost a complete absence of reactions to histoplasmin, and that those native Californians who do react are also reactors to coccidioidin and have presumably had coccidioidomycosis.

Finally, there is the relationship of histoplasmin sensitivity to pulmonary calcification, a demonstrable pathologic lesion. Our studies show that 76 per cent of the whole group who have pulmonary calcifications react to histoplasmin inclusive of all age groups, while only 48 per cent of those not showing calcifications have been sensitized to the antigen, again inclusive of the younger age groups who might subsequently develop calcifications. These differences are so great that one must accept the fact that they are positively associated.

None of these studies prove a direct causal relationship between pulmonary calcifications and histoplasmosis. The histoplasmin sensitivity may merely be an index of the over-all problem of pulmonary and systemic mycotic infections. Further studies of the problem of cross-sensitivity among fungus antigens and infections are needed. Further study to establish the exact etiologic agent or agents responsible for the histoplasmin sensitivity and pulmonary calcifications are imperative.

DISCUSSION

In Chart 1 there was observed a marked divergence of the curves of histoplasmin sensitivity and the development of pulmonary calcifications beginning at the 9-year level as charted but which actually develop at about 11 years. This divergence may be due to the interaction of several possible factors, none of which has yet been studied. It is apparent from the observations as a whole that there is a lessened prevalence of sensitivity to histoplasmin and of pulmonary calcification in the older age groups. It would seem quite possible that small lesions may evolve, through calcification and resorption, at a rate greater than the rate of loss of histoplasmin sensitivity, that the calcification of a given lesion might be resorbed before loss of histoplasmin sensitivity occurs. It is also possible that in the postpubescent groups calcification of a given lesion is less likely to occur. It is furthermore possible that repeated stimuli may maintain histoplasmin sensitivity without producing lesions which go on to calcification.

If the suggestive finding of a lessened prevalence of histoplasmin sensitivity in the older groups is substantiated it may also suggest the manner in

which the infection is acquired. It could indicate that older age groups with their more restrained mode of living and less likelihood of intimate contact with the soil are less likely to come into contact with the infectious agent. Also of significance in relationship to this are observations made by the Williamson County Tuberculosis Study[6] group showing that among the strictly rural groups this tendency to falling off of histoplasmin sensitivity in the older age groups is not observed; suggesting that among people who live closer to nature, i.e., the soil, the sensitivity is maintained throughout life.

The age at which sensitivity develops, its absence in the first year of life, is also suggestive that the infection is not a household contagion and that the fungus is not commonly transmitted from one individual to another. The rapid acquisition of sensitization after the child is able to get out and about again points to a source intimate to the soil. If the soil be the source of the fungus, then it is probable that the acquisition of sensitization would occur earlier in rural as contrasted to urban groups. This observation also indicates the need for study of the details of physical geography in relation to sensitization.

These studies seem to have definite significance from the viewpoint of the interpretations of the mass roentgenographic studies now being made and contemplated.

It seems quite certain that in states bordering the western bank of the Mississippi River and the states of the Western Appalachian slope a large part of the pulmonary calcifications are due to some infection other than tuberculosis. It seems that while this relationship is most striking in that area, it is not confined to this area but has a much wider application. Our studies showing levels of sensitivity of 10 to 20 per cent even in the states outside of the high-prevalence area and those of Palmer[4] would suggest that pulmonary calcifications due to mycotic infection are not limited to the western area of coccidioidomycosis and the eastern Mississippi Valley area of high histoplasmin sensitivity.

Personal communications from a number of Army surgeons would seem to indicate that the problem of men developing pulmonary calcifications while in the Service is one which is causing considerable difficulties in the discharge of Army personnel. Routine discharge roentgenograms are bringing out the fact that there are numbers of men who have developed pulmonary calcifications which presumably were not present at the time of induction.

It is also true that many men were classified as 4-F on the basis of having pulmonary calcifications either too numerous or too large to pass military standards. It would seem from these studies that the majority of these were probably not due to tuerculous infection but rather to a benign pulmonary mycosis, already healed beyond reasonably probable breakdown.

If these studies have no other value, they do serve to reinstitute and reemphasize the necessity of employing tuberculin tests or the demonstration of tubercle bacilli in establishing the diagnosis of tuberculosis in minimal and noncavitated pulmonary lesions and in the healing lesions with pulmonary calcifications.

SUMMARY

1. The subject of the concurrence of pulmonary calcification and histoplasmin sensitivity is reviewed and the accumulated observations concerning this are presented.

2. The age relationships in the development of histoplasmin sensitivity, pulmonary calcifications, and tuberculin sensitivity have been presented.

3. The geographical variations of histoplasmin sensitivity, pulmonary calcifications, and tuberculin sensitivity in more than 1,000 children and young adults resident in Tennessee are shown.

4. The geographic variations in histoplasmin sensitivity, pulmonary calcifications, and tuberculin sensitivity as demonstrated by 611 college students residents of Tennessee and 644 college students residents of various states of southeastern United States and Pennsylvania, New Jersey, and New York have been shown.

5. The significance of histoplasmin sensitivity as demonstrated in these studies has been discussed.

6. The significance of these studies in relationship to the study of the epidemiology of tuberculosis is discussed.

We are greatly indebted to members of the Williamson County Tuberculosis Study and to the Tennessee State Health Department, particularly to Dr. Ruth Puffer, who gave us valuable assistance in the tabulations and statistical analysis of the material; to Drs. R. S. Gass and E. F. Harrison, who read the roentgenograms and made many pertinent and useful comments on the study; and to Commissioner R. H. Hutcheson for his general aid and encouragement.

We are also indebted to the staff of the Vanderbilt University Student Health Service, particularly to Dr. Tom Zerfoss and Dr. Alvin Keller, who made it possible for us to include observations on Group II in our study.

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ELECTROPHORETIC PATTERNS OF BLOOD SERA IN POLIOMYELITIS AND GUILLAIN-BARRÉ'S DISEASE (ENCEPHALOMYELORADICULITIS)

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NORMAL blood sera and plasmas have been carefully studied electrophoretically by Longsworth, Shedlovsky, and MacInnes,[1] Scudder,[2] Moore and Lynn,[3] and by Dole.[4] These investigators have reported the normal composition of the serum and plasma proteins and the relative amounts of the electrophoretic fractions (albumin, alpha globulin, beta globulin, gamma globulin, and fibrinogen) present.

Tiselius[5] first determined the order of migration of the protein fractions of plasma. He used horse serum buffered at pH 7.7 and found the order of migration to be albumin, alpha globulin, beta globulin, fibrinogen, and gamma globulin. Stenhagen[6] then showed that a similar order of migration held true in human plasma.

In the diagrams obtained for the descending boundary in the U-shaped electrophoresis tube a disturbance is commonly observed in the beta globulin boundary, showing up as a very narrow and sharp peak. The cause of this beta disturbance is as yet unknown. Dole[7] states that 14 of 15 normal subjects showed this beta disturbance, and the fifteenth showed it on repetition. Furthermore, one subject showed the beta disturbance on 19 of 20 runs, the one exception being when the blood was not drawn as a fasting sample.

Numerous reports of characteristic changes[1, 8-12] in the electrophoretic patterns of the blood sera in various pathologic conditions have appeared in the recent medical literature. However, in so far as we have been able to determine, there have been no data published on the electrophoretic patterns of sera from cases of poliomyelitis or of Guillain-Barré's disease (encephalomyeloradiculitis). It seemed possible that a study of the sera of cases of these diseases might reveal some characteristic changes in the electrophoretic patterns. The present study was undertaken to determine whether such changes could be demonstrated.

METHODS

The sera investigated were taken, with a few exceptions, from patients in the Department of Pediatrics of the University of Minnesota Hospitals. The blood specimens drawn were all morning, fasting specimens.

The sera were dialyzed for three days at a temperature of 4° C. against a phosphate buffer of pH 7.65 and ionic strength of 0.1, the buffer being changed each day and the final dialysis being made against the total volume of buffer

From the Department of Pediatrics and the Division of Agricultural Biochemistry of the University of Minnesota.
Paper No. 2295, Scientific Journal Series, Minnesota Agricultural Experiment Station.

TABLE I

DETERMINATION NUMBER	NAME	AGE	SEX	DIAGNOSIS	DAYS AFTER ONSET	CHANGE IN BETA DISTURBANCE	SPLIT OF ALBUMIN PEAK	ELEVATION OF INTERPHASE	pH	PARALYSIS
1	M. D.	9	M	Normal*	–	0	±	–	7.65	None
2	J. R.	5	M	Normal†	–	0	–	–	7.65	None
3	M. Z.	15	F	Normal‡	–	0	–	–	7.65	None
24	R. S.	9	M	Normal†	–	0	–	–	8.0	None
41	J. O.	6	F	A. A. P.§	6	1+	±	–	7.65	Slight
10	A. G.	4	F	A. A. P.	8	2+	–	+	7.65	Moderate
36	G. P.	8	M	A. A. P.	8	0	±	–	7.65	Slight
4	M. T.	11	F	A. A. P.	10	2+	±	+	7.65	Slight
37	R. S.	9	M	A. A. P.	10	3+	–	+	7.65	None
38	J. R.	12	M	A. A. P.	11	2+	+	+	7.65	None
39	R. R.	8	M	A. A. P.	11	3+	–	+	7.65	None
5	D. L.	5	M	A. A. P.	14	2+	±	+	7.65	Moderate
40	G. P.	8	M	A. A. P.	19	1+	+	–	7.65	Slight
9	J. B.	9	M	A. A. P.	26	2+	–	+	7.65	Moderate
7	L. L.	4	M	A. A. P.	51	2+	–	–	7.65	Moderate
6	V. B.	15	M	A. A. P.	54	1+	+	+	7.65	Moderate
17	J. P.	6	M	A. A. P.	100	2+	+	–	7.65	Moderate
25	M. T.	11	F	A. A. P.	107	1+	–	–	8.0	Slight
16	H. D.	13	M	A. A. P.	113	3+	–	+	7.65	Severe
15	M. M.	14	F	A. A. P.	119	3+	+	+	7.65	Severe
30	D. L.	5	M	A. A. P.	238	1+	+	+	7.65	Moderate
34	J. Z.	19	F	A. A. P.	238	3+	–	+	7.65	Severe
31	P. M.	9	F	A. A. P.	258	1+	±	+	7.65	Severe
18	E. J.	14	F	A. A. P.	260	0	±	–	7.65	Moderate
33	H. S.	23	F	A. A. P.	300	2+	+	+	7.65	Severe
11	S. C.	21	M	A. A. P.	11 mo.	3+	–	+	7.65	Severe
32	D. A.	4	F	A. A. P.	40 mo.	1+	+	+	7.65	Severe
21	J. K.	19	F	A. A. P.	14 yr.	2+	±	–	7.65	Slight
12	B. W.	25	M	A. A. P.	18 yr.	3+	–	+	7.65	Severe
28	J. S.	24	M	A. A. P.	22 yr.	1+	+	–	7.65	Severe
43	T. H.	42	M	Guillain-Barré	11	1+	+	–	7.65	Severe
42	J. K.	13	M	Guillain-Barré	60	1+	+	–	7.65	Severe
35	D. G.	39	M	Guillain-Barré	75	2+	–	–	7.65	Severe
8	G. C.	9	M	Guillain-Barré	223	1+	+	–	7.65	Severe
29	R. M.	24	M	Guillain-Barré	18 mo.	1+	+	+	7.65	Slight
26	M. P.	15	F	Paralysis of unknown etiology	197	0	–	–	7.65	Severe
27	C. M.	12	M	Pseudohypertrophic progressive muscular dystrophy	9 yr.	0	–	–	7.65	Severe weakness

*Stenosis of larynx.
†Fracture of femur.
‡Suspected chorea.
§Acute anterior poliomyelitis.

required to fill the electrode chambers of the electrophoresis cell. At the end of dialysis the sera were cleared by centrifugation and diluted with three volumes of the buffer against which they had been dialyzed.

The electrophoretic patterns of these diluted sera were then obtained after 9,000 seconds of electrophoresis under a potential gradient of 5.33 volts per centimeter by the "schlieren scanning" method of Longsworth.[13]

EXPERIMENTAL

The cases studied included 23 cases of poliomyelitis, 5 cases of Guillain-Barré's disease, one case of pseudohypertrophic progressive muscular dystrophy, one case of paralysis of unknown etiology, and 4 "normals." These "normals" included one stenosis of the larynx, two fractures of the femur, and one case which was being observed for possible minimal chorea. These "normals" were run primarily as a check on the method, but also to determine whether the normal curves presented in the literature were applicable to children. It was found in all cases that the amounts of the various electrophoretic components corresponded very closely to the normal values found in the literature. The beta disturbance was present in each case as a very narrow and sharp peak.

Table I shows a tabulation of the cases studied.

Calculations of the proportions of the various electrophoretic components present did not reveal any consistent differences between normal and pathologic sera.

However, as shown in Table I, there were some striking changes in the beta disturbance. In the table these changes are classified as 0 to 3+, where 0 is taken to mean no change in the normal beta disturbance and 3+ is taken to mean the complete disappearance of the beta disturbance. 1+ is taken to mean a definite diminution of the beta disturbance and 2+ to mean a very marked decrease of the beta disturbance but not its complete disappearance. Fig. 1 illustrates characteristic patterns for each type.

From Table I it will be noted that there are 26 electrophoretic determinations here reported on the sera of 23 cases of poliomyelitis. Three of these determinations, Nos. 25, 30, and 40, are follow-up determinations on the sera of patients Nos. 4, 5, and 36, respectively. The results of these three pairs of determinations are especially noteworthy and will be discussed briefly.

In the first of these cases blood was drawn from the patient (M. T.) on the tenth day after the onset of symptoms of acute anterior poliomyelitis and again on the one hundred and seventh day after the onset. The first of these determinations (No. 4) showed a 2+ change in the beta disturbance, whereas the second (No. 25) showed only a 1+ change in the beta disturbance.

In the second of these cases (D. L.) blood was drawn on the fourteenth day (No. 5) and again on the two hundred thirty-eighth day (No. 30) after the onset of symptoms of acute anterior poliomyelitis. The first of these determinations (No. 5) showed a 2+ change in the beta disturbance, whereas the second (No. 30) showed only a 1+ change. The electrophoretic diagrams of this case are shown in Fig. 1, where *B* and *C* show, respectively, determination No. 30 (two hundred thirty-eighth day) and determination No. 5 (fourteenth day).

†Fracture of femur.
‡Suspected chorea.
§Acute anterior poliomyelitis.

In the third of these cases (G. P.) blood was drawn on the eighth day (No. 36) and on the nineteenth day (No. 40) after the onset of symptoms of acute anterior poliomyelitis. The first of these determinations showed no essential change from the normal beta disturbance. The second of these determinations, eleven days later, showed a definite (1+) change in the beta disturbance. These two electrophoretic diagrams are shown in Fig. 2.

It may be seen from these three cases that changes in the beta disturbance became less conspicuous after a considerable period of time than they had been

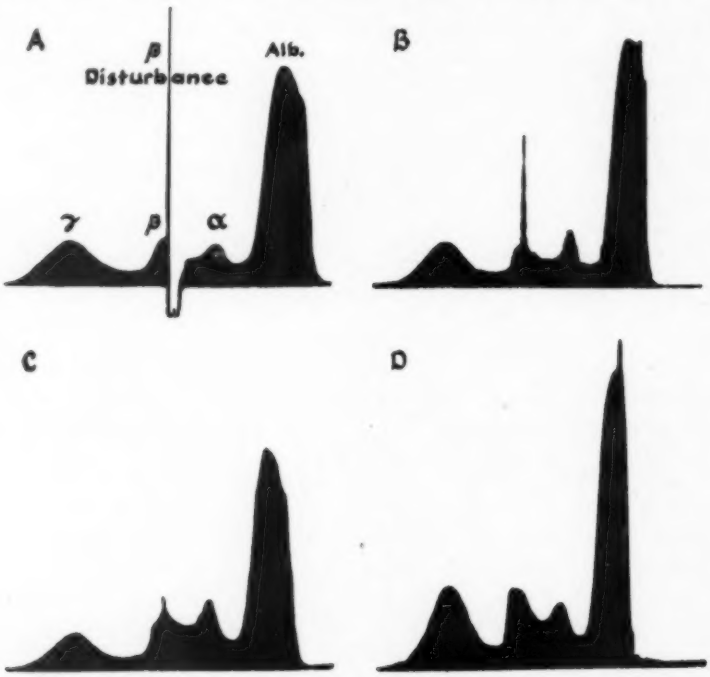

Fig. 1.—Typical electrophoretic patterns illustrating the changes that occur in poliomyelitis. *A*, normal (No. 1); *B*, 1+ change in beta disturbance (No. 30); *C*, 2+ change in beta disturbance (No. 5); *D*, 3+ change in beta disturbance (No. 15).

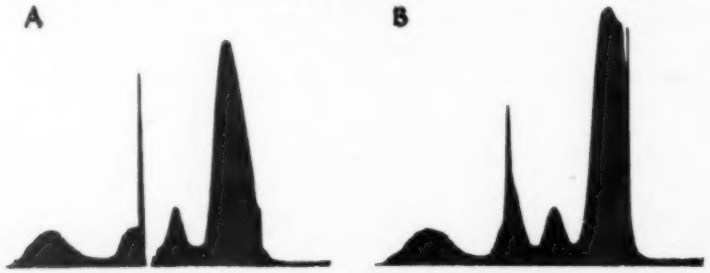

Fig. 2.—Change in electrophoretic pattern of blood serum of poliomyelitis patient (G. P.) with time after onset of symptoms. *A*, 8 days after onset; *B*, 19 days after onset.

earlier in the course of the disease (M. T. and D. L.) and that relatively early in the course of the disease the change in the beta disturbance increased with time (G. P.).

From Table I it will be noted that in all determinations of electrophoretic patterns of the sera of patients known to have had poliomyelitis, with the exceptions of determinations Nos. 36 and 18, there were definite deviations from the normal noted in the beta disturbance. Determination No. 36, as mentioned before, was on the eighth day after the onset of symptoms and was apparently too early in the course of the disease, in this particular case, to detect changes in the beta disturbance, since on the nineteenth day there were definite changes detected. Determination No. 18, on the other hand, was on the two hundred sixtieth day after the onset of the illness. Although in certain other cases the changes in the beta disturbance persisted over longer periods of time than this, it seems possible that changes in the beta disturbance had occurred earlier in the course of the illness but had disappeared by this time.

It will also be noted from Table I that there were apparent deviations from the normal in the beta disturbance as early as six days and as late as twenty-two years after the onset of symptoms of poliomyelitis. There was no correlation between the degree of change and the time since onset of illness. Also there was no apparent correlation between the degree of change in the beta disturbance and the severity of symptoms.

Two other variations from the normal electrophoretic pattern were apparent in the electrophoretic patterns of the sera of patients with poliomyelitis in some instances, but not consistently enough to be considered significant. These were: (1) a splitting of the albumin peak and (2) an elevation of the alpha-globulin-beta-globulin interphase (that part of the curve between the alpha-globulin peak and the beta-globulin peak). The first of these variations is well illustrated by Fig. 1, *B* and the second by Fig. 1, *C*.

The five cases of Guillain-Barré's disease (encephalomyeloradiculitis) studied gave results entirely similar to those of the poliomyelitis cases. The electrophoretic patterns obtained in these cases were in no way distinguishable from those obtained in the cases of poliomyelitis.

On the other hand, the case of pseudohypertrophic progressive muscular dystrophy and the case of paralysis of unknown etiology included in this report yielded electrophoretic patterns which corresponded well with the normal serum pattern and had none of the characteristics shown by the patterns of sera from cases of poliomyelitis and of Guillain-Barré's disease.

While the incidence of a marked degree of abnormality of the beta disturbance in the patterns obtained on poliomyelitis and encephalomyeloradiculitis sera is a very positive finding, the interpretation of this fact and its significance with regard to these diseases must remain in doubt. There is evidence[14] that the disturbance is associated with a weak lipoprotein complex existing in the components of the beta globulins which becomes partially dissociated when the beta components are under the influence of an electric field in the absence of the albumin and alpha globulin components of the serum (i.e., in the descending

leg of the electrophoresis cell). The conclusion that the dissociation tendency of this lipoprotein complex is changed as a result of these diseases would seem obvious, but an accurate interpretation of this phenomenon must await a clearer understanding of the true nature of the beta disturbance as it occurs normally.

SUMMARY

1. Electrophoretic study was made of the blood sera of 4 "normal" children, 23 cases of poliomyelitis, 5 cases of Guillain-Barré's disease (encephalomyeloradiculitis), 1 case of pseudohypertrophic progressive muscular dystrophy, and 1 case of paralysis of unknown etiology.

2. All of the electrophoretic patterns of the sera of the "normal" children agreed well with those in the literature for adults.

3. All of the cases of poliomyelitis, with a single exception, showed definite abnormalities in the beta disturbance, although the time from onset of illness ranged from 6 days to 22 years.

4. In one case of poliomyelitis no abnormality in the beta disturbance was noted at the eighth day of illness but there was a definite abnormalitiy at the nineteenth day.

5. In 2 cases of poliomyelitis there was a definite decrease in the abnormality of the beta disturbance after periods of ninety-seven days and two hundred and twenty-four days had elapsed following the first determination.

6. The electrophoretic patterns of the sera of patients with Guillain-Barré's disease (encephalomyeloradiculitis) did not differ appreciably from those of patients with poliomyelitis.

7. Electrophoretic patterns of the serum of the one patient with pseudohypertrophic progressive muscular dystrophy and of the one patient with paralysis of unknown etiology were within normal limits.

8. Calculations of the proportions of the various electrophoretic components present did not reveal any consistent differences between the normal and the pathologic sera studied.

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THE BABY GRID*

An Application of the Grid Technique to Growth and Development in Infants†

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FOR the purpose of brief and immediate definition, the Baby Grid may be described as a direct-reading, control chart on the quality of growth and development in individual infants. It is based on the principles, collectively referred to as the Grid technique,[1] which have been extensively explained in studies on malnutrition,[2] and in reports on other types of growth failure in older children.[3]

Up to the advent of the Grid, the need for a method such as this to evaluate growth in school children had long been felt. Since then, the wide acceptance and interest[4] with which the Grid has been received, and the systematic application[5] to which it has been put during the past five years have fully confirmed that need. Experience has demonstrated that quality control on growth can be achieved in practice by this simple means. One advantage, which has come to be very apparent and valuable to those who have actually worked with Grid records of older children, is the capacity of the big Grid to pictorialize the growth and development of a child and to do this in such a way as to make the quality of growth self-evident at almost a single glance. This same advantage is found in Baby Grid records of individual infants.

Despite the natural importance of infant growth and despite the high degree of interest that it attracts, the corresponding need for quality control on the growth and development of babies is somewhat obscured by the success of modern infant feeding and care. Since pediatrics has been quick to utilize the results of research on nutrition and to apply methods of preventing disease, improved health has been followed by improved growth. Superficially, at least, the hazards to growth would seem to have disappeared along with the hazards to health, but not, of course, to the point where bigger and better babies can be guaranteed by "rubber stamp" prescriptions. Babies are far too individualistic, and their growth is always too much at the mercy of force

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†This study is the outcome of earlier investigations which suggested the possibility of applying the principles of the Grid technique to the growth of infants as small as 1,000 Gm. premature babies.[5] Significant as this evidence then was, it seemed best to delay publication of the Baby Grid until proof could be assembled that would be independent of clinical considerations and based on measures other than those of weight and length alone. The demonstration[6] that Grid levels are lines of constant body surface over an even more extended range (down to the 1 Gm. embryo) furnished the necessary fundamental support that was sought. Various aspects of this result were first given before the Northwest Pediatric Society, St. Paul, Minn., May 4, 1945, and in the Frederick A. Packard Memorial Lecture, Philadelphia, Pa., May 8, 1945. Further amplification with data on body volume and specific gravity were reported to the Cleveland Physics Society, Cleveland, Ohio, Oct. 4, 1945.[6] The five-color Baby Grid was presented and discussed before the American Association of Physical Anthropologists April 2, 1946.

and counterforce to permit anything but continued individual care. This being so, they will also continue to require individual control of their growth and development.

Accordingly, the need for checking infant growth is not lessened simply because infant feeding has been successful, or because good results have been observed without benefit of precise methods for evaluating growth. In fact, the practical need for close control is even more urgent than in former times. Once the example has been set, the responsibility for attaining top quality is obviously increased, and it therefore becomes still more important to know how well a given baby is fulfilling his own capacity for growth.

DIFFICULTIES IN THE USUAL TYPES OF APPRAISAL

A baby's health, physical condition, and progress are so related that his feeding and care are governed to a large extent by what can be determined about his growth and development. For this purpose, information is sought, as a rule, from three sources: (1) history and physical examination of the baby, (2) clinical experience, as a background for evaluating the findings, and (3) body measurements such as weight and length, among others. In arraying the evidence from these different sources, certain difficulties are always encountered, and a brief explanation of them will indicate what the Baby Grid has been designed to overcome.

If judgment is based solely on (1) and (2), it is formed entirely of subjective impressions that are more appropriate to the evaluation of the baby itself, as reflected by the medical findings of his physical condition, than to conclusions on his growth, which, in this case, are exceedingly indirect. Therefore, to obtain data on growth as a distinct element, weighing and measuring babies has become permanently established as a pediatric procedure.

Nevertheless, even though weight and length have the advantage over physical findings of being objective representatives of body changes associated with growth and development, they convey much less information than is expected of them. In other words, the basic measurements of weight and length which are taken for the purpose of making clinical judgment more certain, do not carry their own significance with them. What that is must be elicited by some method of treating the data.

However, the usual methods of dealing with a baby's measurements have yielded so little information as to throw doubt on the practical value of the data, and, unfortunately, to discourage the practice of weighing and measuring babies. When this is done, it eliminates the only objective support that clinical judgment can command.

While full details concerning this unsatisfactory situation have been given elsewhere,[2, 3] the main causes can be stated briefly. For instance, the only asset a simple weight curve possesses is its internal consistency, and yet even regularity may be misleading. Furthermore, to compare a baby's weight with the usual standards is technically incorrect, as ought to be evident from the very individualism that babies display. This, in fact, excludes the right to apply age averages of whatever kind, whether means, medians, or percentiles,

in tabular or curve form, because these fail, among other things, to make due allowance for individual differences in physique, an item that cannot be disregarded in attempting to appraise either a baby or his growth.[2] Although such standards are in common use today, the time and effort involved are hardly repaid, since the results are given no serious consideration.

Moreover, comparing two separate age curves of weight and length in order to obtain an idea about body build is confusing, particularly if the data are charted in deviation form. These methods leave the identification of so concrete an attribute too much to the imagination, especially since it is possible, as the Baby Grid shows, to determine physique very precisely and to display the results without ambiguity. Finally, empirical rules, such as doubling the birth weight in from five to six months and tripling it in a year, fall far short of providing adequate guidance.

Thus the traditional methods of dealing with weight and length, which involve matching the values of a given baby with tables, curves, or rules of one kind or another, have failed to be useful because they do not at the same time include a suitable basis for interpreting the measurements of individual babies. To be specific, they do not supply standards for judging the quality of individual growth performance.

OBJECTIVES

In view of the foregoing, the broad practical purpose of the Baby Grid is to bring out the significance of an infant's measurements so as to make the interpretation of the results not only objective but also as accurate and as obvious as possible. Its particular aim is to deal with the ever-recurring question of whether growth and development in a given infant is or is not satisfactory. Put otherwise, this is simply a matter of determining the quality of growth. Consequently, the purpose of the Baby Grid is to furnish the yardsticks, the standards of individual performance, and, in brief, a self-contained method for measuring, recording, and displaying the quality of growth directly. It seeks to make a baby's growth and development more nearly the guide to infant feeding and care that they are supposed to be.

RANGE OF OPERATION

As previously shown,[5, 6] the principles of the Grid technique operate throughout the long span of human development marked at its lower end by an embryo weighing 1 Gm. and at the other by the most extreme examples of gigantism and obesity. Within this interval the Baby Grid provides a control chart on the quality of infant growth and development between birth and 3 years. As such, it applies not only to the case of full-term infants but also to premature babies weighing as little as 1,000 Gm. or having a body length of only 12 to 13 inches.

Consequently, by establishing these standards of performance in its own field, and by uniting them into a single formulation of law and procedure that holds both for premature as well as for full-term infants, the Baby Grid bridges a gap that has remained open until now.

EVALUATION OF GROWTH QUALITY IN INFANTS

Preliminary Approach.—Even without previous description, the curves of Figs. 1 to 7 illustrate how simply the quality of an infant's growth may be ascertained and recorded by plotting his weight and length on a Baby Grid from time to time. The results, in fact, are practically self-evident, since the significance of the original measurements is directly revealed in terms of the fidelity with which the curves of these different infants conform to certain obvious patterns of the Grid. Where the basic trends are followed, one infers without second thought that growth quality is, and has been well controlled; the steadier the curves, the more certain this conclusion. Where trends break, even the first stages of deviation are readily recognized, and they are sufficient to place the quality of growth in question; the greater the departures, the more certain it is that growth is not under control and therefore faulty.

Structure of the Baby Grid.—Panels *A, B, C* in Fig. 1 contain the channel system, *1* to *5*, the standard schedules of development (auxodromes) numbered *7*, *8*, and *9*, and energy scales, respectively. All these operate just as they do in the Big Grid for older children.

Panel A. The Channel System: As before, the plan of the channel system provides a field or map in which the position of points plotted from the original measurements of a baby's weight and length (scales *a*, *b*) may readily be identified by channel and by cross-graduated levels (*6*).

In the Baby Grid, however, there are two parts to the channel system: the left half, *3*, *4*, *5*, represented by channels A_{12}-A_5 is required because babies do not normally travel along the main line of human development represented by the right half, *1*, *2*, the original A_3-*M*-B_3 group of this compound system. They travel these side tracks of infancy because they are naturally more chubby than the older children on the main line or than they themselves were during intrauterine life.[6] The direction of the course they take through the channel system is indicated by the central (yellow) shaded path, *3*, *4*, *5*. Thriving premature babies traverse the lower portion, *3*, which joins the full-term strip where the weight-length points of normal newborn infants are found, *4*. Thenceforward the path is strictly up-channel until it begins to bear right on its way toward re-entry on the main line. The turn, *5*, is reached in about eleven to twelve months by average babies.

The purpose of the channel system is again threefold: (a) to act as a kind of direction finder for ascertaining the *trend* of a baby's own curve as

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Fig. 1.—The Baby Grid (front). Panels *A*, *B* contain the channel system or grid proper, *1*, *2*, *3*, *4*, *5*, the standard schedules of development, *7*, *8*, *9*, for advanced, average, and premature babies, respectively. Panel *C* contains the scales for energy requirements and energy quotients; *a*, weight scale in kilograms and pounds, *b*, length scale in centimeters and inches; *c-d* the channel curve of a baby girl twin, *e-f* the corresponding auxodrome obtained by plotting the levels of respective points in the channel system, Column 5 against age, Column 2. Note ample space allowance for the newborn period, *e*. D, E, subsidiary panels for charting chest and head circumferences, Columns, 6, 7. Thriving premature babies follow the shaded path, *3*; the weight-length points of "average" full-term infants are found in the region, *4*; *5*, the upper turn of the infant path usually reached at 11-12 months; *6*, level lines of development which measure the size of a baby in terms of body surface, see table of Useful Data lower left, and reproduction, Table II. The diminishing numerical values of these level lines indicate that the baby is approaching more and more closely to the end of infancy, *d*, about level 0. The quality of growth and development as revealed by the curves, *c-d* and *e-f* in comparison with the trends of the path 4-5-*d* and of the standard *8*, is consistently satisfactory.

NAME Mary Ann L.

BIRTH DAY 5/20/43 PLACE Ch. DR. Jones

The Baby Grid

A Guide to Individual Progress during I

DATE	AGE	WEIGHT	LENGTH	LEVEL	HEAD	CHEST
5/20/43	B	5-8	48¾	182	34.5	29.5
5/27/43	7½d	5-2	49	189	—	—
6/5/"	16d	5-7½	49.5	182	—	—
7/1/"	6w	8-2½	21½	142	34.8	34.0
8/21/"	3m	10-¾	23½	112	38.5	35.5
10/4/"	4½	13-2	25½	92	39	37
11/20/"	6	15-4	26½	78	40½	41
2/19/44	9	17-10	28	61	44	43
4/21/"	11	19-2	29¼	52	44.8	44.7
8/18/"	15	21¾	30½	39	45.5	—
2/19/45	21	24-6	32½	26	47.3	—
12/23/"	30	27-7	36	11	48.0	—
5/18/46	36	30-1	38¼	0	49.0	—

USEFUL DATA

Level	Body Surface sq. M.	Blood Vol. Total cc.	Blood Vol. Plasma cc.	DIET Grams Usual Formulas* Carb	DIET Grams Usual Formulas* F,P	DIET Grams Human Milk C-F-P	Thiamin Niacin × 10 mg.	Riboflavin mg.
280	694	75	45	18	4 7½		08	12
260	108	90	54	20	5 8½			
240	123	108	65	23	6 9½		10	15
220	140	166	78	26	7 10½			
200	160	156	94	30	7 12½		13	20
190	171	170	102	32	8 12½			
180	183	187	112	35	11		16	24
170	196	205	123	39	12	35-16-6		
160	209	225	135	43	13	39-18-6	19	28
150	224	247	148	47	14	42-19-7	21	32
140	239	270	162	52	16	46-21-8		
130	256	298	179	57	17	51-23-8	25	38
120	273	325	195	62	19	56-26-9		
110	292	356	215	69	21	62-29-10	31	46
100	312	392	235	75	23	67-31-11	34	51
90	334	430	258	83	25	74-34-12		
80	357	470	282	92	28	81-38-14	41	62
70	381	515	310	101	31			
60	408	566	340	107	33		48	72
50	436	595	372	117	36		52	78
40	466	685	410	125	38			
30	498	749	448	136	42		60	90
20	532	840	495	146	45			
10	569	915	540	156	48		70	1.05
0	608	1000	595	168	52		75	1.13
+10	650	1100	650	180	55			

*50-55-10% of Cal. from Level + Cal. Scale as Fat-Protein; 45-50-5% of Calories in Carb.-Fat-Protein

Vitamin A	1000	2000 I.U.	Fe	6.00	7.00 mg.
Vitamin D	400	800 I.U.	Cu	0.60	0.70 mg.
Ascorbic Acid	20	40 mg.	Mn	0.75	3.75 mg.
Ca 0.8- 1.0, P 1.1- 1.4 gm.			I	0.01	0.04 mg.

Inches 20 22 24 26

Cm. 50 55 60 65

A B C D

Physique Channels

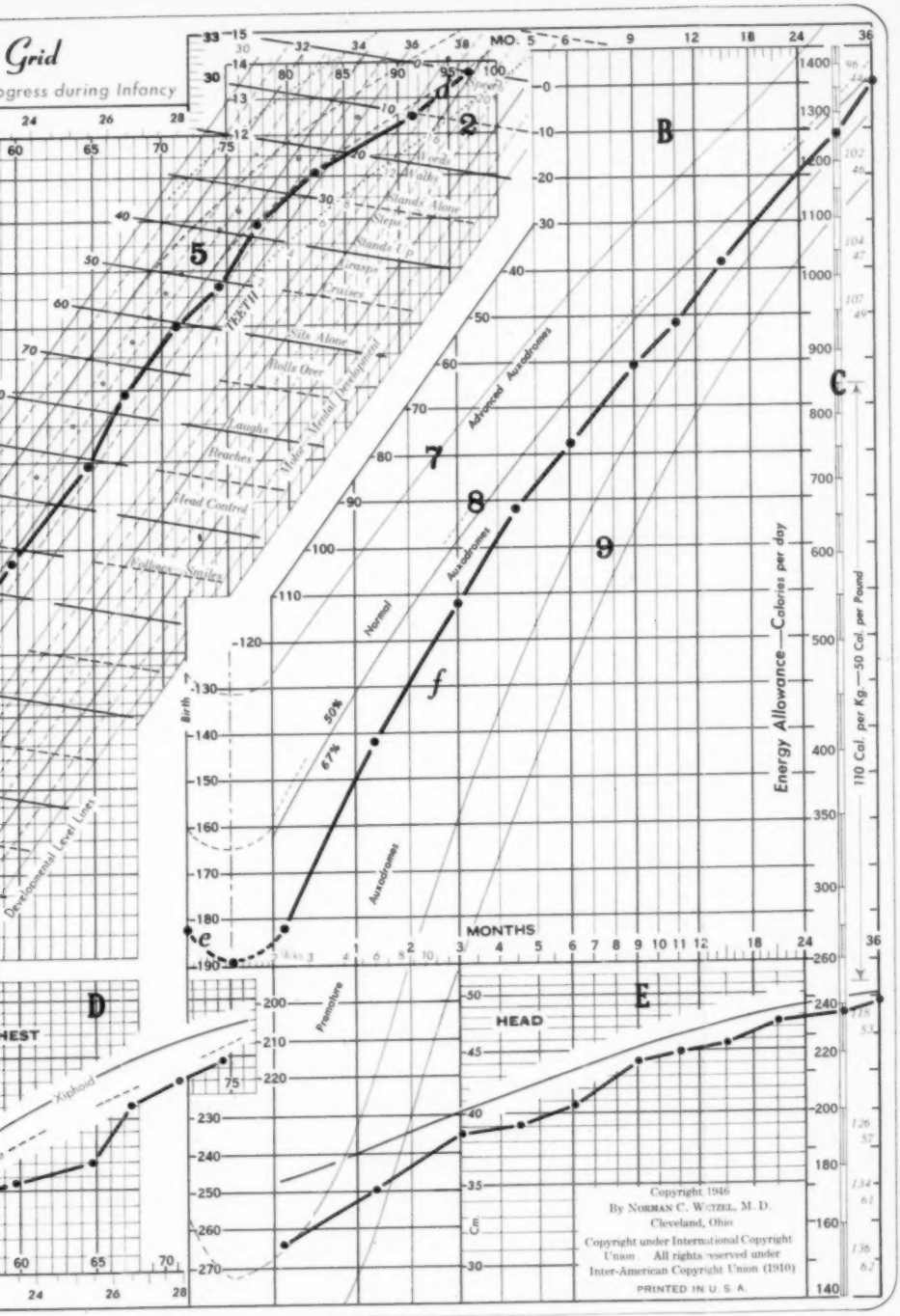
Developmental Level Lines

Kg Pounds WEIGHT

CHEST Xiphoid Nipple

40 Cm. 45

LENGTH Inches 18 20 22 24 26


Grid
ogress during Infancy
MO.
MONTHS
Energy Allowance—Calories per day
110 Cal. per Kg.—50 Cal. per Pound
Birth
Normal
Autodromes
Advanced Autodromes
50%
67%
Premature
HEAD
CHEST
Xiphoid
Developmental Level Lines
Follows Simply
Head Control
Reaches
Laughs
Makes Mental Developments
Rolls Over
Sits Alone
Stands Alone
Walks
Words
Praises
Grasps
Stands Up
Steps
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plotted from the data on weight and length; (b) to measure a baby's *size* by means of the level at which various weight-length points are located, for each level represents a different value of body surface[6*] and (c) to identify a baby's *physique* or shape by the channel the points fall into, chubbiness increasing in channels toward the left and slenderness toward the right in accordance with the scheme of Table I.

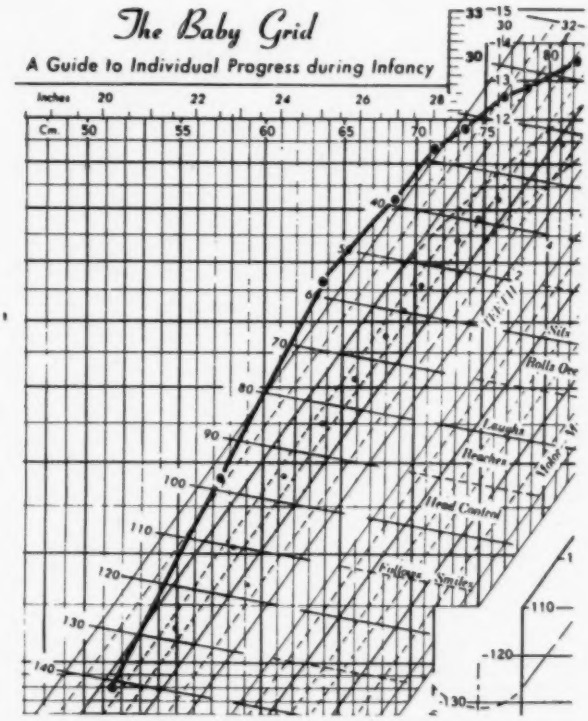

Fig. 2.—Typical response to overeating. A good robust baby in A_{10} at Level 141, getting fatter as his curve proceeds outward. Extremely fat at Level 60. Note, however, that he rounded the curve in normal fashion at levels that would be expected from his earlier course. Mother "poured food into him."

Although a baby's size (surface) obviously increases as he proceeds along the channel system (Table II) the numerical value of the level lines diminishes. This indicates simply that, as a baby advances, he is coming closer and closer to the end of infancy at about level 0.

As a guide to the closely associated events of motor-mental development, the appearance of *smiling, head control, rolling over, sitting, standing,* etc., is indicated by labels in the right hand channel system at the levels of physical development where these events may normally be expected to occur. Their inclusion in this schedule form should help to focus attention upon, and to emphasize the connections between physical, mental, and motor development.

*See introductory footnote.

TABLE I.—THE "PHYSIQUE-SPECTRUM" OF THE CHANNEL SYSTEM IN A BABY GRID SHOWING SIGNIFICANCE OF VARIOUS CHANNELS

	BABY CHANNELS—(GREEN)								PRE-SCHOOL CHANNELS		CHANNELS FOR SCHOOL CHILDREN—(RED)							
	A_{12}	A_{12}	A_{11}	A_{10}	A_9	A_8	A_7	A_6	A_5	A_4	A_3	A_2	A_1	M	B_1	B_2	B_3	B_4
Level lines ↑	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---
				Yellow Band														
	Fat, Big Babies			Average build Normal build Medium build			Thin Long Tall		Transition from baby chubbiness to childhood slenderness		Stocky		Medium build Normal build Average build			Fair	Borderline	Poor
	SIDETRACKS OF INFANCY										MAIN LINE OF HUMAN DEVELOPMENT							

Tooth eruption, expressed as number of teeth expected at corresponding levels of physical development, is indicated along the lower edge of the baby channels by the series of red italic numerals: *1, 2, 4, 6,* etc., at levels *62, 48, 42, 35,* etc., respectively.

Panel B. Schedules of Development (Auxodromes): Basically, this panel is a distance-time chart in which the horizontal lines are actually extensions of the level lines originating as cross-graduations in the channel system. The curve formed by plotting a baby's level in the channel system against his age will tend to parallel one of the near-by schedules, *7, 8, 9,* which represent performance standards on the speed of development for babies of different grades of advancement. The fullest possible allowance is thus made from birth on for the tremendous differences between large full-term babies whose curves are near, *7,* babies of "average" advancement, *8,* and tiny (1,000 Gm.) premature infants, *9.*

*Panel C. Energy Relations:** Total fuel requirements in calories per day are scaled to the level lines. Energy quotients may be read similarly.

Accessories: Two subsidiary panels permit graphing head and chest circumferences. Twenty sets of observations (*date, age, weight,* etc.) may be entered in conveniently ruled data space. A table, reproduced here as Table II and arranged by steps of ten levels, gives the corresponding numerical values for various items as *body surface, total blood* and *plasma volume, diet composition,* etc. The reverse side of a Grid has space for biographical and clinical notes, and contains an entry table for immunizations and tests.

*Although energy relations to infant and child growth have been studied for almost fifty years and are today part of the pediatrician's daily work, they have been ignored by most nonpediatric students of child growth. The fundamental connection between level and calorie requirements established in the Grid technique in 1940 is explained by the more recent demonstration (see introductory footnote) that levels are lines of constant body surface. The irrelevant basis of the criticism which Bruch[7] projected has been disclosed elsewhere.[3] Meanwhile the results of Stuart and his co-workers,[8] reporting an elaborate fifteen-year study at the Harvard School of Public Health covering 5,916 diet records of 269 children from 1 to 10 years old, have appeared. When these are compared with the corresponding Grid estimates of fuel requirements, the agreement is statistically exact.[6] This verification of the level-calorie relations in the Grid technique is all the more remarkable because of the entirely independent origin of the results.

Regarding fuel requirements in infants it may be noted (1) that these are read directly from the scale in Panel C, Fig. 1 and Fig. 6, that is, 160 calories per day at level 260, and 1,050 at level 37 and (2) that these values assure energy quotients of the order specified in the accompanying scale; 135 and 104 calories per kilogram, respectively, for the examples mentioned.

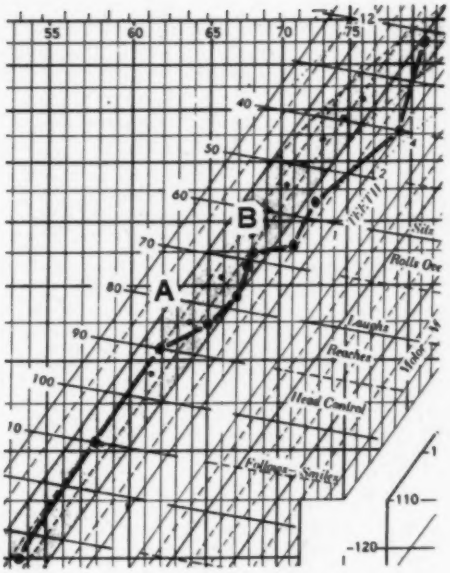

Fig. 3.

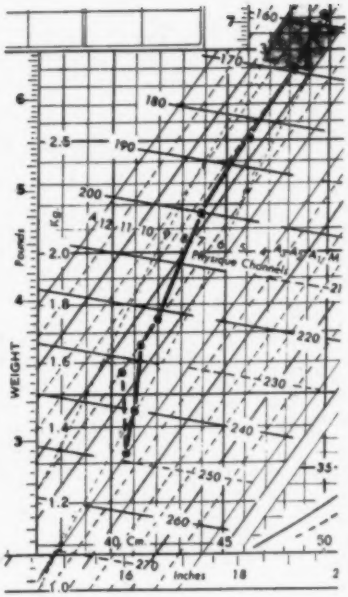

Fig. 4.

Fig. 3.—Clear-cut channel shifts: *A*, at the time this boy's father went to war; *B*, measles. Note subsequent complete recovery to central path, as expected.

Fig. 4.—The path of an initially small, but later, of a thriving premature baby. Physiologic loss followed by excellent reorientation of direction.

TABLE II

USEFUL DATA

Level	Body Surface	Blood Vol. Total	Blood Vol. Plasma	DIET—Grams Usual Formulae* Carb	F,P	Human Milk C-F-P	Thiamin, Niacin: x 10	Riboflavin
	sq. M.	cc.	cc.				mg.	mg.
280	.094	75	45	18	4-7†	.....	.08	.12
260	.108	90	54	20	5-8†	.....	.09	.13
240	123	108	65	23	6-9†	.....	.10	.15
220	140	130	78	26	7-10†	.....	...	...
200	160	156	94	30	7-12†	.....	.13	.20
190	171	170	102	32	8-12†	.....	...	...
180	183	187	112	35	11	.....	.16	.24
170	196	205	123	39	12	35-16-6	...	...
160	209	225	135	43	13	38-18-6	.19	.28
150	224	247	148	47	14	42-19-7	.21	.32
140	239	270	162	52	16	46-21-8	...	...
130	256	298	179	57	17	51-23-8	.25	.38
120	273	325	195	63	19	56-26-9	...	...
110	292	358	215	69	21	62-29-10	.31	.46
100	312	392	235	75	23	67-31-11	.34	.51
90	334	430	258	83	26	74-34-12	...	...
80	357	470	282	92	28	81-38-14	.41	.62
70	381	515	310	101	31	.....	...	...
60	408	566	340	107	33	.....	.48	.72
50	436	595	372	117	36	.....	.52	.78
40	466	685	410	125	39	.....	...	...
30	498	740	445	136	42	.....	.60	.90
20	532	840	495	146	45	.....	...	...
10	569	915	540	156	48	.....	.70	1.05
0	.608	1000	595	168	52	.....	.75	1.13
+10	.650	1100	650	180	55	.....	...	...

*50-35-15% of Cal. from Carb. - Fat. - Protein.
Cal. Same as Human Milk.
151-29-20% of Calories as Carb.-Fat.-Protein.

Vitamin A	1000—2000 I.U.	Fe	6.00—7.00 mg.
Vitamin D	400— 800 I.U.	Cu	0.60—0.70 mg.
Ascorbic Acid	20— 40 mg.	Mn	0.75—3.75 mg.
Ca	0.8–1.0; P 1.1–1.4 gm.	I	0.01—0.04 mg.

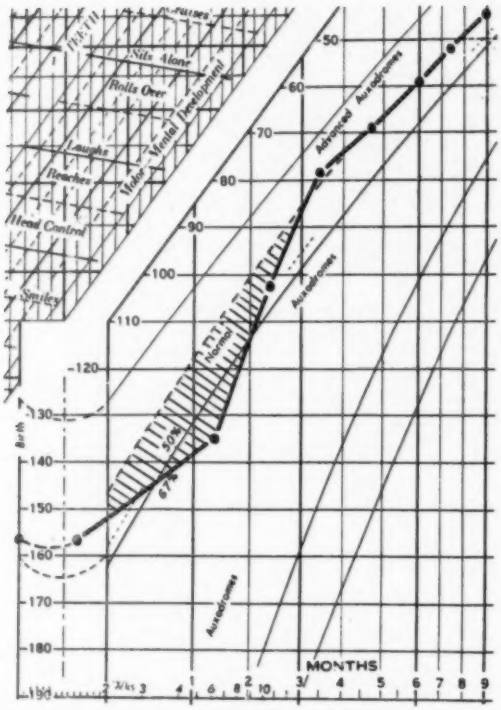

Fig. 5.—Slow start in a baby with feeding difficulty. Recovery after the sixth week and thereupon steady progress along auxodrome expected on basis of birth weight.

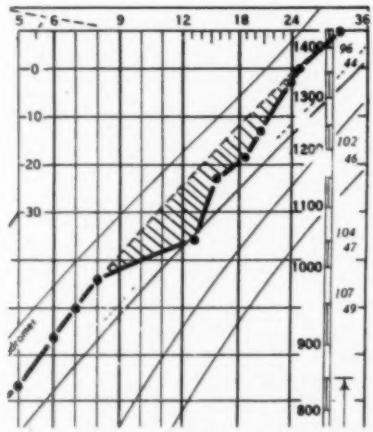

Fig. 6.—Excellent adherence to own auxodrome up to the eighth month when family was forced to undergo repeated changes of residence. Dashed projection shows expected auxodrome. Cross-hatched area proportional to fuel debt.[3] Vertical distances between expected and actual auxodrome measure lag, that is, the number of levels the baby is in arrears at a given age. Full recovery when home had been resettled.

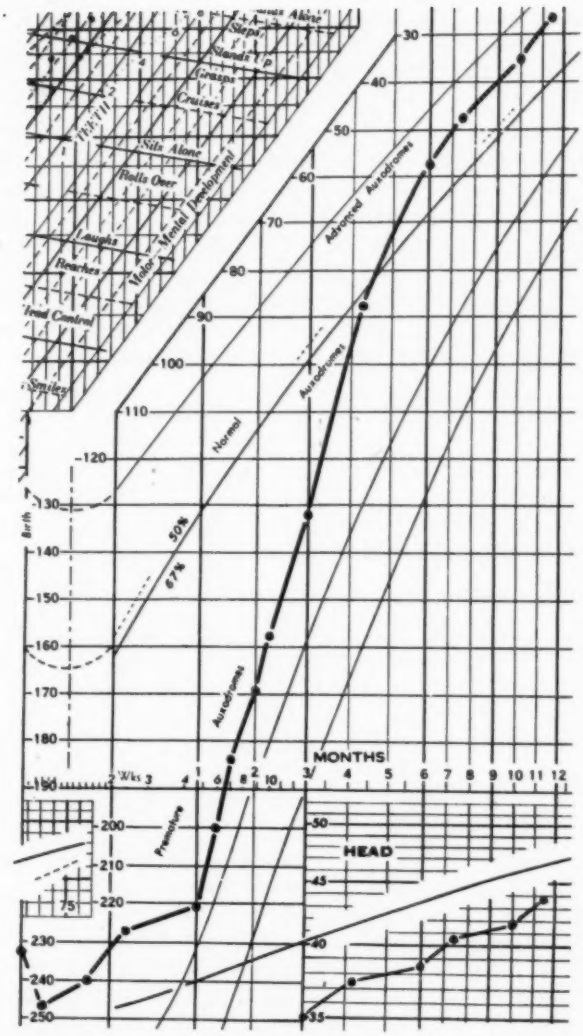

Fig. 7.—The auxodrome of the premature baby in Fig. 4. After the first month's difficulties in getting started, this baby made up time (and distance) to proceed at normal speeds along a comparatively advanced auxodrome after the age of 6 months.

DIRECTIONS

To make out a Baby Grid record proceed as follows: (Compare Fig. 1.)

Step 1. Record name and birth date above ruled table at upper left. Enter date of observation, age, weight, length, head and chest circumferences.

Step 2. Plot weight against body length in Panel *A*. Use vertical (*a*) scale for either kilograms or pounds and ounces, and horizontal (*b*) scale for centimeters or inches.

Step 3. Read *developmental* level from black diagonal scale along green channel system and insert the value in Column 5 of ruled table.

Step 4. Plot level as just read against corresponding age in Panel *B* to locate position of baby's auxodrome.

Repeat steps one to four for each observation and draw the curves point to point. Complete record by plotting chest circumference against body length in Panel *D* and head circumference against age in Panel *C*.

To use Motor-Mental Development Scale note that a baby may normally be expected to follow objects when he has reached level 108; to roll over at level 65; to take steps with help at level 32, etc.

To use Calorie-Intake Scale read value corresponding to a given level.

Suggestions: For results such as are illustrated in Figs. 1 to 7 which are shown full size, use medium pen and black ink. Check all apparent deviations. When a baby's auxodrome deviates as in Figs. 5 and 6, sketch in the expected auxodrome with a dash line and cross-hatch the lag area in red crayon or ink for maximum contrast.

PRINCIPLES OF INTERPRETATION

Direction and Speed of Development.—The key to the problem of evaluating growth as well as to the mechanism of the Baby Grid is found in the pertinent but often neglected fact that growth is a *moving* and not a *static* function in babies, or for that matter in any organism.[3] It is for this reason that a mother asks, intuitively, how her baby "is doing," rather than how he "is." This fact also explains why it is more significant to know, not what a baby weighs or how long he is, but instead, what that baby is accomplishing with the weight and length he does have.

A baby's growth, then, is best characterized in terms of its *direction* and *speed*. This, however, implies two things: (1) methods for measuring direction and speed, and (2) tolerance limits by which it is possible to determine whether direction and speed in a given infant, and throughout a given interval, conform to standards of performance shown by actual experience to be acceptable. Both (1) and (2) are furnished as a single procedure in the Baby Grid.

The direction of a baby's development is revealed with the help of the channel system, and the acceptability of a given direction is defined in terms of individual channel width. Thus, for example, many infants will follow the direction of the channel system over the straightaway portion of their course so precisely that point after point will fall not merely within the narrow limits of the same channel, no matter which this happens to be, but almost exactly

on the very same line. That is top quality direction. Ordinarily, shifts of one channel in twenty levels of forward advancement are acceptable, but even these should not persist. Normally, they will be compensated after an equal forward advance. On the turns, a baby's curve should follow the trend of the shaded pink and yellow path with corresponding certainty.

Similarly, in the case of speed, a baby's auxodrome ought not fail, without good explanation, to keep within two to three levels of running parallel with a near-by standard.

Quality Control of Growth in Individual Infants.—The question as to whether a particular infant is, or is not doing well is therefore very directly answered so far as objective information is concerned by noting (*a*) how closely that baby's curve in the channel system is following the direction of *all* healthy babies at the same stage or level of development, and (*b*) how nearly the baby is keeping up with one of the standard schedules; that is, whether it is progressing from level to level as rapidly as is called for by that schedule of development.

Direct quality control on growth may therefore be considered as established when an infant's measurements have actually been made to demonstrate that the direction and speed of his development are both being maintained within the foregoing tolerance limits of allowable variation. Fluctuation within these limits is due solely to chance. By contrast, deviations outside these limits indicate, apart from frank errors, that the departures should be considered the result of trouble, and hence that the babies who fail this test of quality should be examined for cause. (See Figs. 2, 3, 5, 6 and 8.)

RESULTS

The curves in Figs. 1 to 7 illustrate typical problems that are encountered in practice.*

*The examples and results illustrated here in Figs. 1 to 7 have been selected from a series of about 1,800 Baby Grid records under current study. No attempt is made to classify this series further, since the results could reflect merely local conditions at the moment and since they could not possibly have any bearing on the accuracy or the validity of the Baby Grid. This point should be emphasized because the question is sometimes raised as to how many "cases" have been employed "to test" the Grid technique. Consideration of the methods used to develop this technique will help to explain the limitations of any admissible tests: The operation of the Baby Grid involves two fundamental principles and two only, namely, the direction and speed of human development; other principles, such as are involved in the question of physique, size, and energy relations, are subsidiary.

As regards direction, the data of the past 100 years covering the range of human development from embryonic life to stages of gigantism are sufficient to determine this direction to within 43 seconds of arc.[3, 6] Moreover, it can be shown that any significant deviation from this will ultimately lead to abnormal body contours. The principle of shape, and the designation of shape by channels, is merely a consequence of this extremely precise orientation of growth. One does not, therefore, attempt to channelize babies or children; they actually do this themselves by maintaining the fundamental direction of development, which, incidentally, differs by only 1 degree 3 minutes of arc from the direction typical geometrical bodies would take, if they, too, developed to greater sizes.[6]

As regards speed, it may be remarked that early (1875-1900) data on breast-fed infants conform well to present auxodrome standards, but that the contemporary observations on artificially fed babies do not meet these standards satisfactorily. As presently conducted, artificial feeding does support the same speed of development characteristic of healthy breast-fed babies.

Consequently, the demonstration that a baby does or does not follow these basic norms of direction and speed is not so much a test of the Grid as it is of the baby. Since it would be possible to select any number of babies who do follow the Grid standards, as well as any number who do not, at least over certain intervals, such selections remain arbitrary and cannot decide for or against those elements that are intrinsically a property of human development.

It may, nevertheless, be added that recent data from large-scale studies so ably and faithfully assembled by Krogman[3] all bear out the Grid specifications of direction and speed, a result that is plainly apparent in the original data of Quetelet reported more than a century ago, and in all major observations since then.[3]

Direction.—The steady forward course of the baby girl twin in Fig. 1 shows how closely a healthy, thriving infant will maintain a channelwise direction of development along the straightaway, and hence a constant physique over that portion of the path. Her curve along the lower border of the yellow path, that is, along A_7, represents a degree of chubbiness that remains consistently just less than average but hardly enough less to call slender or thin.

By contrast, the curve in Fig. 2 shows a boy getting overly fat because his mother kept "pouring food into him" in the belief that he, like the rest of the family, was living to eat. The opposite effect is shown by the curve in Fig. 3. This boy started out well as an average baby. He fell victim to his father's going to war at *A*, and to measles at *B*, but finally recovered his expected central channel position.

The small premature baby in Fig. 4, after his initial loss to level 249 in A_4 where he looked "scrawny," steered an excellent uneventful course through the shaded path, thereby becoming five and one-half channels more robust and chubby at level 158 in A_9 than he had originally been.

Speed.—The auxodrome of the twin in Fig. 1 conforms to the neighboring standards, *8* and *9*, on either side of it. At point after point this baby reached expected levels on time. Following a good start, speed of development was up to par.

The curve of Fig. 5 is that of a baby with feeding difficulty whose start was slow but whose development picked up sufficient speed to enable him to proceed along his own schedule after the tenth week.

In Fig. 6, excellent progress up to the eighth month is interrupted by several cross-country changes of residence, a few minor infections, and a generally unsettled home. Speed is lost during the slow-down but is accelerated during recovery. At normal speed the baby would have continued to progress along the upper broken projection. The cross-hatched area between this as the upper and the actual auxodrome as the lower border is proportional to the fuel debt[3] which must be made up preliminary to full recovery. Vertical differences between expected and actual auxodromes measure the amount of lag in levels at any given age, as 36-21, or fifteen levels of lag at 13½ months, but only about five at 21 months.

The auxodrome of Fig. 7 is that of the small premature baby whose channel course is shown in Fig. 4. After the first month's difficulties had been overcome the infant made up for lost time, ultimately finding his own proper schedule by the age of 6 months. While most premature babies will follow along in the region between standards *8* and *9* (Fig. 1) a few, such as the baby of Fig. 7, will manifest a tendency to reach and thereafter to pursue more advanced schedules without in any sense being pushed to do so. Such infants, it may reasonably be assumed, would have been equally advanced had they gone on to term.

REMARKS

The foregoing examples in Figs. 1 to 7 taken together show how simple it is, by means of the Baby Grid, to apply the principles of direction and speed

to the problem of evaluating the quality of growth in individual infants, despite great differences in their types, size, and age. Besides illustrating how notably uniform growth and development normally are, these examples also demonstrate how soon a given departure can indicate that growth is unacceptable, or at least in question. In all of these cases, they illustrate the manner in which a baby's growth can routinely support clinical estimates of his condition and thus serve as an objective guide to the management of his feeding and care.

SUMMARY

The Baby Grid is a direct-reading, control chart on infant growth including that of premature babies weighing as little as 1,000 Gm. It has been designed to pictorialize the growth and development of a given infant during its first three years, and to do this so as to make the quality of growth self-evident at a single glance.

Babies are too individualistic and their growth too much at the mercy of force and counterforce to permit anything but individual care, and accordingly, individual control of their development. Attainment of top quality presumes knowledge on how well a given baby is fulfilling his own capacity for growth. The answer to this ever-recurring question of pediatrics is directly revealed in terms of the fidelity with which a baby's measurements of weight and length conform to the Grid standards of direction and speed of physical development. These are the decisive elements to be evaluated because of the pertinent but often neglected fact that growth is a moving, not a static function in babies. The Baby Grid thus seeks to make an infant's growth more nearly the objective guide to the management of his feeding and care that it is supposed to be.

ADDENDUM

A striking example of how the Baby Grid pictorializes the bizarre effects on infant growth and development that must be expected from the profound disturbance caused by the dual lesion—congenital adrenal cortical insufficiency associated with macrogenitosomia due to hypersecretion of androgenic hormone—is obtained from the data in Thelander's recent report,* which summarizes the history of a boy followed from birth, whose course up to 14 months had been described earlier,† and who died at 6 years of age in an attack of measles. These papers furnish a unique set of observations along with measurements on body weight and length, the resulting Baby Grid record for the first two years being shown in Fig. 8.

Since only three values for body length up to 14 months were reported, in comparison with many measurements of weight, linear interpolation was employed to estimate length at ages for which weights, but not lengths, were given. This procedure was clearly justified by the consistency of the original length measurements which were distributed at almost equal intervals between birth and 14 months and which formed a smooth, not an erratic, curve. Full

*J. PEDIAT. 29: 213, 1946.
†J. PEDIAT. 18: 779, 1941.

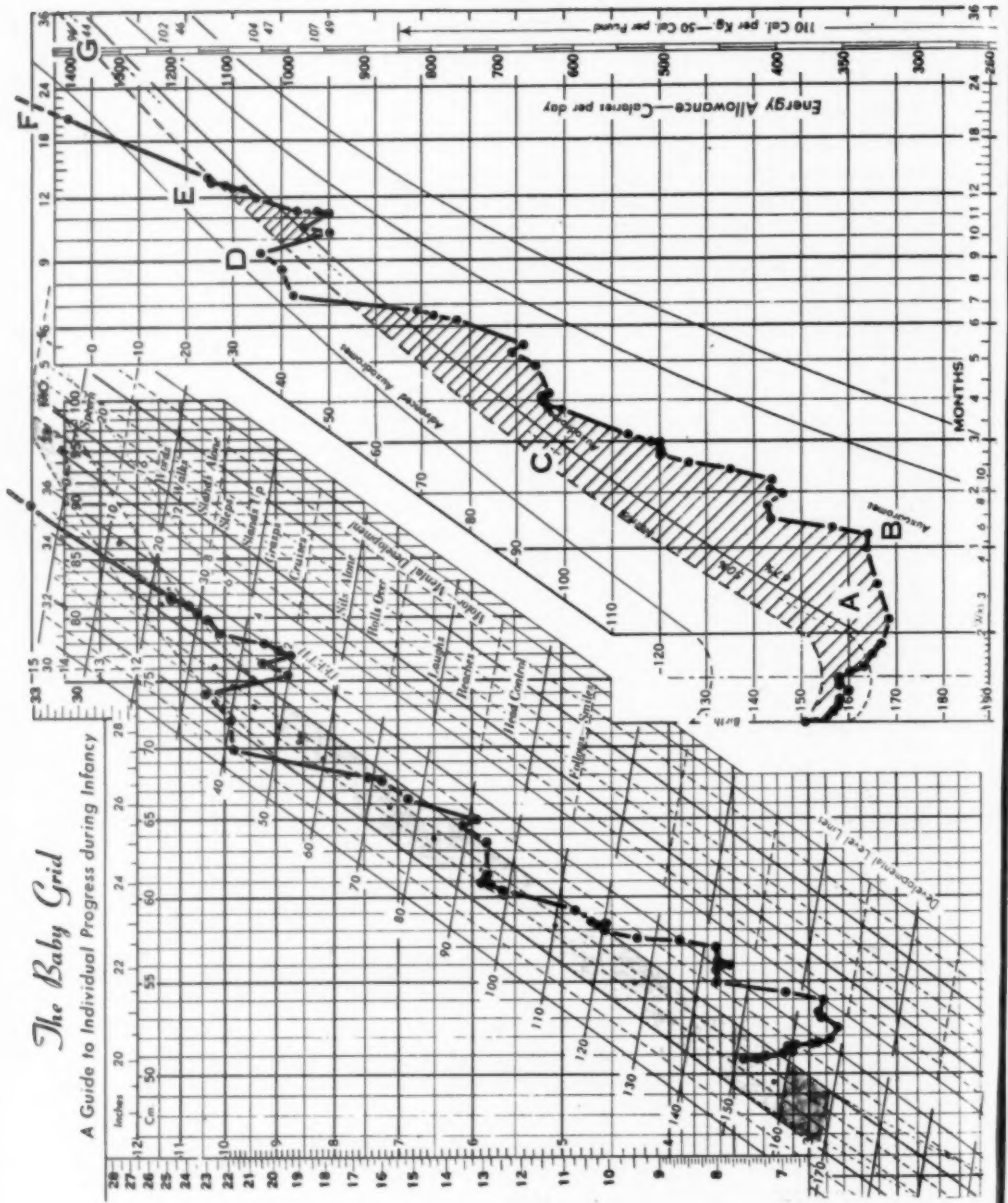

Fig. 8.—(*For legend see opposite page.*)

use could thus be made of the weight data so that Fig. 8 represents the best Grid estimate that can be constructed out of the known facts.

Viewed as a whole, the curves in Fig. 8 clearly reflect not only the fundamental trends and tendencies of growth and development in this unusual affliction but also the effects of treatment as well. Particularly noteworthy and instructive are: (1) instability, attributable, no doubt, to the defective water-salt-hormone metabolism; (2) prolonged neonatal failure to initiate growth until Percorten was administered; (3) dependence of growth on continued administration of the hormone in some form; (4) severe reaction to an otherwise mild attack of exanthem subitum; and (5) a two- to threefold increase in the rate of physical development. The latter enabled the infant to regain a 42 level lag handicap at 1 month by the time he had reached the age of 7½ months. Following his roseola (9-13 months) it also had the effect of propelling him at almost triple speed far beyond his "expected" levels, 8 and +7, respectively, at 2 and 3 years, as represented by the dashed auxodrome.

His later course graphed on a Big Grid and discussed more fully in forthcoming articles* shows that this uninhibited burst of speed persisted after the lag-gap had once been closed at 14 months so that he reached level 115 by the age of 6 years, that is, a level attained by a boy on the 67 per cent auxodrome at 12.75 years. From 1 to 7½ months, high speed was mainly a "recovery" phenomenon; but the continued surge of the auxodrome between 14 and 24 months, as well as thereafter, must be ascribed to overproduction of androgenic hormone, since the effects it represents compare with the results that are found in early gigantism. Contrary to Thelander's opinion, based on the height-age curve, that this boy's "ultimate height . . . would have been below average," Grid analysis of these data would, if anything, suggest ultimate gigantism, provided, of course, that the epiphyses remained open. For the auxodrome of Thelander's patient is, in fact, headed almost directly toward the same point reached by a notable pituitary giant, namely, A_1–189 at 9 years![6] So far as the growth data go there is nothing up to the last observation at 6 years to suggest that the auxodrome was within a year or so of reaching its upper limit in spite of advanced bone age findings. Accordingly, there is no Grid basis for expecting premature closure as a result of impending gonadotropic action. It seems altogether more likely that this boy was destined for excessive rather than for curtailed stature.

Apart from these implications, the curves of Fig. 8 as compared with the steady trends in Fig. 1 afford an excellent illustration of great differences in

*In preparation for *Brenneman's Practice of Pediatrics*, Irvine McQuarrie, Editor, W. F. Pryor Company, Inc., Hagerstown, Md.; and for *Therapeutics of Infancy and Childhood*, Harry R. Litchfield and Leon Dembo, Editors, F. A. Davis Company, Philadelphia.

Fig. 8.—Unstable growth and development in congenital adrenal cortical insufficiency associated with macrogenitosomia as reconstructed from the recent data by Thelander discussed in the addendum to this paper. Note prolonged failure to regain birth level, *A*, until Percorten was administered, *B*, at about the sixth week; thereafter, a definite but somewhat irregular recovery to more central channel pathways (improved physique) as well as to expected auxodrome, *C*, lag-gap being closed at 7½ months. Reaction, *D-E*, due to exanthem subitum. Path, *E-F*, shows persisting elevation of speed resulting in attainment of levels far in advance of expected segment, *E-G*. Segment, *B-E*, a "recovery" phenomenon; segment, *E-F*, the first clear evidence of a spurt that continued unabated until 6 years and that was in all probability due to oversecretion of androgenic hormone.

"growth quality" within the limits of attainable control and of how simply these effects may be portrayed.

The author is particularly indebted to Miss Mary E. Sweeny and to Miss Marian E. Breckenridge of the Merrill-Palmer School, Detroit, for placing many of their long-term careful records at his disposal. The final stages of design and construction of the Baby Grid were greatly expedited by this opportunity to study their data objectively and then to compare the results with their personal observations and histories of those infants and children.

The author is also greatly indebted to Drs. Spencer A. Wahl, Joseph E. McClelland, John D. Nourse, and Robert B. Hauver for their kindness in providing case observations made under the conditions of actual practice.

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   (c) Scramlin, E. Nancy: Hoosier Health Herald **27**: 83, 1946.
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5. Child Growth and Development Emphases in Teacher Education, Prepared by the 1943-1944 Teachers College Collaborators, Lonzo Jones, Chairman, American Association of Teachers Colleges, p. 23. (Systematic use of the Grid in School Medical Health Service such as recommended in this report is being carried out in various communities, notably: In Oneonta, New York, under the direction of Dr. Francis H. Marx, Director of School Physicians; in the Delta County Schools, Escanaba, Michigan, under supervision of C. P. Titus, Commissioner; in Crawford County, Ill., Bryan Heise, Director of Extension Service; in Detroit, Citizen's Evaluation Study Committee, Arnold K. Meier, Director; in Corpus Christi, Texas, Independent School District, M. P. Baker, Superintendent.) Similar large-scale use of the Grid is being made by Captain I. T. Thacker in Boy's Brigades, Physical Training Battalion, Kimberley, South Africa; in the School Districts of Clayton, Mo., Everett, Mass., Winston-Salem, N. C., Grant's Pass, Ore., Shaker Heights and East Cleveland, Ohio. For pediatric appraisal the Grid is being employed in various institutions and departments such as: The Laboratory Schools, University of Chicago; St. Louis Children's Hospital; and Henry Ford Hospital, Detroit.
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THE EFFECT OF DIABETIC AND PREDIABETIC PREGNANCIES ON THE FETUS AND NEWBORN INFANT

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IT HAS long been recognized that the diabetic state in the mother has often been associated with many unusual phenomena in the fetus and newborn infant. Among the outstanding peculiarities of these infants there has been noted a high mortality rate, a tendency toward an excessive birth weight and occasional anatomic changes in some of the viscera and glands of internal secretion. Until recently it has been thought that these peculiarities of the offspring were in large part related to the maternal hyperglycemia and the manner in which it was regulated. The excessive size of the fetus was attributed directly to the fact that the fetus was maintained during pregnancy on a high carbohydrate intake. The high fetal mortality was explained either by the occurrence of maternal hyperglycemia or hypoglycemia associated with an inadequate regulation of the diabetes; the high neonatal mortality was considered to be the result of the hypoglycemia induced in the newborn infant by the overactivity of its pancreatic islet tissue. The basis for this theory rested on the observation that in some infants born to diabetic mothers an actual hypertrophy of the islet tissue could be observed. Recent studies indicate that these previously held theories are improbable. There is considerable evidence to show that all the phenomena observed in infants born to diabetic mothers are to be found among infants born before the onset of maternal diabetes. It is the purpose of this paper to review not only this newer evidence but also the recent investigations that have been made on the etiology of the high fetal and neonatal mortality in diabetic pregnancies.

FETAL AND NEONATAL MORTALITY

The frequent occurrence of fetal deaths before the appearance of diabetic symptoms was first noted by Allen.[1] His findings were corroborated in a study by Miller, Hurwitz, and Kuder.[2] Data taken from the latter report are given in Table I to show the effect of the prediabetic state on the fetal and neonatal mortality rate. The mothers of the infants included in Table I all developed diabetes during the childbearing period and gave birth to infants both before and after the onset of diabetes. It is seen that the fetal and neonatal mortality was about as high during the twenty years preceding the onset of maternal diabetes (19.8 per cent) as it was after the syndrome made its appearance (23.6 per cent). It has also been shown by Miller[3] that there was a high fetal and neonatal mortality rate among the offspring of women even though the mothers

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did not develop signs and symptoms of diabetes until after they had reached the fifth and sixth decades of life. The data in Table II are taken from this latter report by Miller. The data in Table II indicate that among infants born less than sixteen years before the onset of maternal diabetes to women who have passed the childbearing period there was a high fetal and neonatal mortality rate (15.9 per cent). Recently Herzstein and Dolger[4] have published data which support the findings in Tables I and II, although their conclusions are at variance with their statistics. They concluded from their findings that "the first five-year prediabetic period revealed an increased fetal and neonatal mortality, but the preceding 15 years was not characterized by such a tendency." Their data show, however, a mortality of 7.5 per cent among 212 infants born during the fifteen years prior to the onset of diabetes in the mothers. This rate is statistically significantly higher than the rate of 3.01 per cent in a group of 398 infants born to nondiabetic women to which they were compared. Herzstein and Dolger failed to see the significance of their own data, partly because they chose to compare mortality rates based on personal interviews with the diabetic mothers, held in some instances many years after the deliveries took place, with infant mortality rates of control groups based on hospital deliveries and actual records made at the time the deliveries occurred.

TABLE I. MORTALITY AMONG FETUSES AND NEWBORN INFANTS DELIVERED DURING PREDIABETIC AND DIABETIC PERIODS

	BIRTHS	FETAL AND NEONATAL DEATHS	DIED (%)
Prediabetic period			
1-5 yr. before onset	79	28	35.4
6-10 yr. before onset	79	10	12.6
11-20 yr. before onset	94	12	12.7
Total before onset	252	50	19.8
Diabetic period	93	22	23.6

TABLE II. FETAL AND NEONATAL MORTALITY OF INFANTS DELIVERED BY WOMEN DEVELOPING DIABETES DURING THE FIFTH AND SIXTH DECADES COMPARED WITH THAT OF INFANTS DELIVERED BY NONDIABETIC WOMEN

	BIRTHS	FETAL AND NEONATAL DEATHS	DIED (%)
Prediabetic period			
1-15 yr. before onset	63	10	15.9
16 yr. or more before onset	201	12	6.0
Total before onset	264	22	8.3
Nondiabetic controls	263	5	2.0

It is not easy to determine the exact onset of diabetes in adults and on that account the mortality rates given for the prediabetic infants are open to criticism. However, the fact that the mortality rates were found to be high ten, fifteen, and twenty years before the onset of recognizable signs and symptoms, particularly as is demonstrated in Table I, tends to obviate the criticism that the date of onset of the diabetes cannot be absolutely stated.

BIRTH WEIGHT

The tendency toward an increased birth weight among infants born to diabetic mothers is recognized by all. A similar tendency prior to the inception of maternal diabetes has been noted both by Allen[1] and Miller, Hurwitz, and Kuder.[2] Miller[3] has also shown that the birth weight of the infant was increased even though the onset of maternal diabetes was delayed until the fifth and sixth decades of life. In Table III are presented data taken from the latter study. The statistics are the result of an investigation into the birth weight of infants born to women who were admitted to the New Haven Hospital with a history of having had an onset of diabetes after they had reached 40 years of age. No infants were included in the study unless they had been born in the New Haven Hospital. The data were few, since the chances were small that a woman would enter the New Haven Hospital with an onset of diabetes after 40 years of age and would have been delivered in the same hospital several years before. No infant who weighed less than 2,500 grams at birth or who was a twin was included. In spite of the small number of births obtainable it is thought that the results are of considerable significance. Three of the twenty-two infants reported in Table III weighed over 5 kg. at birth; six weighed over 4.5 kg. and fifteen weighed 4.0 kg. or more. The incidence of infants in the various weight groups are approximately 200, twenty-seven, and seven times greater, respectively, than the expected ratios for normal newborn infants in the same birth weight categories.[5, 6] The average birth weight of the twenty-two infants in Table III is significantly higher than that of a control group studied in the same hospital.[3]

TABLE III. BIRTH WEIGHT OF TWENTY-TWO INFANTS BORN TO SIXTEEN WOMEN DEVELOPING DIABETES IN THE FIFTH AND SIXTH DECADES

YEARS BEFORE ONSET OF MATERNAL DIABETES			
20-16 YR.	15-11 YR.	10-6 YR.	5-1 YR.
BIRTH WEIGHT (KG.)			
3.0	3.6	4.0	4.2
3.2	3.7	4.1	4.7
3.2	4.0	4.3	5.5
3.4	4.0	4.6	
3.6	4.1	4.7	
	4.2	5.2	
	4.4		
	5.5		

From the case histories of the mothers of the infants whose birth weights are listed in Table III it was possible to be reasonably sure that the infants were born before the onset of diabetes in their mothers. Information concerning the presence or absence of glycosuria was available on the mothers' histories in twenty of the twenty-two pregnancies. Reducing substances were found in the urine of only three mothers during their pregnancies. In the first of these, the fasting blood sugar was 87 mg. per 100 c.c. of blood, and in the second, 89, 94, and 112 mg. The third mother had three urinalyses for sugar during her preg-

nancy and reducing substances were found in only one specimen. None of the sixteen mothers had signs or symptoms of diabetes at any time during the twenty-two pregnancies.

ANATOMIC CHANGES IN THE VISCERA AND GLANDS OF INTERNAL SECRETION

Two striking visceral changes have been described in some of the infants born to diabetic mothers; these are an increased size and weight of the heart and an excessive extramedullary erythropoiesis. Both of these changes have been observed in infants who have been born prior to the onset of maternal diabetes.[7] Hurwitz and Irving[8] were the first to report the presence of cardiac enlargement in an infant born to a diabetic mother. They also observed an increased amount of glycogen in the myocardium, using Best's carmine stain. More extensive studies of the cardiac hypertrophy have since been made by Miller and Wilson[9] and Miller, Johnson, and Durlacher.[10] It appears from their studies that cardiac hypertrophy is seen at post-mortem more frequently in those infants who have a birth weight over 4.0 kg. than in those who weigh less. Their studies likewise show that considerable cardiac enlargement apparently is compatible with the survival of the infant. Equally interesting is the fact that the enlargement of the heart as demonstrated by roentgen examination is not permanent but tends to lessen gradually, so that by the time the infant is 2 months old the heart is usually normal in size and shape. A similar change in the heart of an infant born during the prediabetic period has been reported by Miller.[7] The possibility that the cardiac hypertrophy might account for some of the symptoms of infants born to diabetic mothers was considered by Miller and Wilson, but they were not able to reach any definite conclusions on that point.

The cause of the cardiac hypertrophy is not known. The finding of increased amounts of glycogen in the myocardium as reported by Hurwitz and Irving and since corroborated by others[10] offers a possible lead for future study. The excess glycogen in the myocardium of some infants born to diabetic mothers is not to be considered in the same category as that found in cases of von Gierke's disease, in which the glycogen is fixed in the cells probably as a result of failure of the enzyme systems to liberate it. More likely the increase in cardiac glycogen in infants of diabetic mothers is related to some metabolic disturbance associated with the maternal diabetes as has been described in diabetic rats by Lackey, Bunde, Gill, and Harris.[11]

The extramedullary erythropoiesis in infants born to diabetic mothers, which is most marked in the liver and spleen, is observed in almost all cases studied at post-mortem.[9, 10] Since most of these infants are either stillborn or die within the first four days after birth, it is not known how long the extramedullary erythropoiesis persists. Studies of the peripheral blood and its normoblast content suggest that, as in erythroblastosis fetalis associated with Rh incompatibility, the extramedullary activity is short-lived. The differentiation between the extramedullary erythropoiesis associated with the blood incompatibilities of the mother and fetus and the extramedullary erythropoiesis seen in infants born to diabetic and prediabetic mothers has given some difficulty to clinicians and pathologists in the past. There are differences, however, which permit one to

make the correct diagnosis in most instances. The infant born to a diabetic mother or prediabetic mother does not become anemic or develop marked jaundice.[10] Macklin has pointed out that the amount of hemosiderin in the livers of infants born to diabetic mothers is small as contrasted to the large amount seen in infants with Rh incompatibilities in whom considerable hemolysis has occurred.[12] Whenever excessive erythropoiesis is encountered in the newborn infant, red blood cell counts, tests for hemosiderin in the tissues, along with the appropriate tests for blood group incompatibility and tests for congenital syphilis are necessary.

Several of the glands of internal secretion have shown anatomic changes, the significance of which is not clear. Hyperplasia of the islands of Langerhans has been known to occur in some of the infants of diabetic mothers since Dubreuil and Anderodias made their report in 1920.[13] It has recently been shown that similar changes in the islet tissue are to be found in infants born to prediabetic mothers[7] and in infants with erythroblastosis fetalis associated with blood group incompatibility.[14, 15] It has also been shown that occasionally there is an increase in the size and weight of the adrenal glands in infants born to diabetic and prediabetic mothers.[7, 10] A similar finding has been reported by Sarason[16] in some infants with erythroblastosis fetalis. An increase in the amount of eosinophilic elements in the anterior pituitary gland has been shown to be present in infants born to diabetic and prediabetic mothers.[7, 17-19] Also, a considerable hyperplasia of the female sex organs has been described.[20, 21]

The information concerning the anatomic changes in infants born to diabetic mothers is incomplete. No systematic examination of the material has yet been made either as to the incidence of the various changes or their possible interrelationships. Sufficient facts are available to demonstrate that the anatomic changes seen in infants born to diabetic and prediabetic mothers are not specific and that there is a surprising degree of similarity between this group of infants and those with erythroblastosis fetalis associated with Rh incompatibility.[10]

One further anatomic change to be noted is the high incidence of infants born to diabetic mothers who exhibit congenital malformations.[22-24] In nineteen consecutive autopsies on infants born to diabetic mothers, six infants were found in whom there were one or more malformations. These six in addition to one other who survived (Case 7) are listed in Table IV. The anomalies reported in Table IV were reviewed by Dr. George W. Corner of The Carnegie Institute of Embryology. It was his opinion that in all instances the malformations were present before the end of the third month of gestation.[25] The significance of

TABLE IV. CONGENITAL ANOMALIES IN SEVEN INFANTS BORN TO DIABETIC MOTHERS

1. Harelip; agenesis of gall bladder; bicornate and septate vagina; hypoplasia of right humerus and femur; agenesis of left femur and fibula; syndactylism; agenesis 12th thoracic vertebra and ribs; sacralization 4th and 5th lumbar vertebrae and fusion of the coccygeal segments
2. Double left ureter with hydroureter and hydronephrosis
3. Cor biventriculare; hypoplasia of aorta
4. Bicuspid pulmonary valve
5. Anencephaly
6. Agenesis of bladder; agenesis of kidneys; incomplete development of ureters
7. Persistent pupillary membranes

these observations is not known but needs to be considered in view of the growing interest in the etiology of congenital anomalies.

ETIOLOGICAL FACTORS

During the past few years there has been an increasing tendency to think of the various phenomena observed in infants born to diabetic mothers in terms of some endocrine disturbance. The increasing knowledge that carbohydrate metabolism is vitally affected by the anterior pituitary gland and the adrenal cortex, as well as by the islands of Langerhans, has naturally focused attention on the possible role of the many hormones secreted by these glands as factors in the etiology of the changes seen in these infants. The excessive birth weight of infants born to diabetic mothers has caused many investigators to speculate that the growth hormone of the anterior pituitary might be not only diabetogenic for the mother but growth-promoting for the fetus. In support of this theory is some experimental work by Young, who showed that the injection into puppies of crude pituitary extract in excess of the amount required to produce diabetes in adult dogs caused an increase in growth rate in the puppies.[26] It is also interesting to consider that the splanchnomegaly seen in infants born to diabetic and prediabetic mothers bears some resemblance to that seen in patients with acromegaly. Cushing and Davidoff[27] described marked cardiac hypertrophy without evidence of arteriosclerosis, generalized enlargement of the adrenal cortex with adenomatous changes and hyperplasia of the islands of Langerhans besides an enlargement of the liver and spleen in patients with acromegaly.

The possible role of some hormonal imbalance as a cause for the high fetal and neonatal mortality rate has been the object of several studies carried out by White and other workers in Dr. Joslin's clinic and by Smith, Smith, and Hurwitz.[28] The latter conclude from their investigations that there is a deficiency in the production of steroid hormones by the placenta during diabetes, which causes fetal death. They have suggested large doses of diethylstilbesterol beginning about the sixteenth week of pregnancy in order to counteract the lagging production of estrogen which apparently occurs in the latter part of some diabetic pregnancies. For similar reasons White and Hunt[29] have tried replacement therapy, using estrogen and progesterone in the last half of pregnancies complicated by diabetes, and reported marked success in lowering the number of fetal deaths. It is too early to judge whether or not the replacement therapy employed by the investigators mentioned is going to be uniformly successful in reducing the high mortality among the offspring of diabetic mothers. More studies will be needed before this treatment can be considered to have passed the experimental stage.

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KERNICTERUS IN ERYTHROBLASTOSIS FETALIS

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THE diagnosis of erythroblastosis fetalis has been made at the New Haven Hospital between 1928 and October, 1945, in the cases of seventy-four infants. Twenty-seven deaths have occurred; there have been twenty-three autopsies. Four surviving members of the series show mental retardation. In an analysis of these cases it was found that a large proportion of the deaths occurred in a characteristic manner and that clinicopathologic correlations of considerable interest existed.

In thirteen of twenty-seven deaths the clinical course has been some variant of the following general pattern. An infant, jaundiced within the first three days of life, with a degree of icterus varying from slight to extreme, displays drowsiness or lethargy and may show mild generalized rigidity or a tendency to assume an opisthotonic position, especially when disturbed. Convulsive twitches or spasms occur less frequently than the signs just noted. The infant takes feedings poorly and may vomit. Edema or a sclerema-like condition of the subcutaneous tissue is present at birth or may develop later. Some time between the second and fifth days of life the condition of the infant becomes very alarming. The respirations are found to be irregular or gasping and the child is cyanotic and in peripheral vascular collapse. Examination of the chest discloses râles and rhonchi throughout the lungs. There may be a systolic murmur in the heart which has not been heard on a previous examination. There may soon appear a discharge of bloody froth or mucus from the upper respiratory tract. Death invariably supervenes in a matter of a few minutes or a few hours.

The occurrence of these signs and symptoms marks a group of fatal cases of erythroblastosis fetalis in all of which kernicterus was present at autopsy. The pulmonary lesion which appeared to account for the respiratory signs was focal hemorrhages. These hemorrhages occur into alveoli and give rise to hemorrhagic foci which are generally seen macroscopically as well as microscopically. There may be very extensive involvement of lung or portions of lung in this process. Table I shows that signs relating to the respiratory system were more frequently seen in these babies than those signs suggesting brain injury. In three infants who showed both lesions at autopsy, there was no note made of signs of central nervous system disorder other than gasping and irregularity of respirations; these may well indicate a brain lesion. Of thirteen babies with focal pulmonary hemorrhages twelve had kernicterus, and the other (Case 15) had a diffuse discoloration of cerebral tissue with yellow pigment without localization in the basal nuclei. There was widespread necrobiosis. Durlacher[1] states that pulmonary hemorrhages of the type encountered in these cases may occur in babies with respiratory difficulties con-

sequent upon intracranial hemorrhage in the newborn period. We and others[2, 3] have seen a predilection for involvement of the medullary as well as the basal nuclei in kernicterus: it may be that this involvement brings about disturbed respiratory dynamics which, with the familiar increase in bleeding tendency[4] in erythroblastosis fetalis, result in pulmonary hemorrhagic phenomena.

The specificity of drowsiness, opisthotonos, rigidity, and motor hyperirritability or dyskinesia as signs of kernicterus is suggested by the fact that of the surviving children in this series who had any of these signs other than drowsiness during the acute phase of erythroblastosis fetalis, all four are mentally retarded and present some motor disability, presumably the sequel of kernicterus. Two other infants with such signs, who survived the acute phase of the illness with severe neurological sequelae, died at 5 months and at 3 years of age, and are included among the patients dead with kernicterus listed in Table I. In both of these children autopsy showed extensive destruction of the basal ganglia.

TABLE I. CLINICAL MANIFESTATIONS IN SEVENTY-TWO CASES OF ERYTHROBLASTOSIS FETALIS

	DROWSINESS LETHARGY	SPASTICITY RIGIDITY	OPISTHOTONOS	CONVULSIVE DISORDER	GASPING IRREGULARITY	RÂLES RHONCHI	BLOODY DISCHARGE FROM RESPIRATORY TRACT	DEVELOPED SYSTOLIC MURMUR	EDEMA
A. Cases with kernicterus									
Dead (16 cases)	7	5	6	4	12	12	9	7	6
Living (4 cases)	3	1	2	2	0	0	0	0	0
B. Cases without kernicterus									
Dead (9 cases)	2*	2*	0	0	3†	2†	0	0	5†
Living (43 cases)	5	0	0	0	0	0	0	0	6

*Includes Case 34, not autopsied.
†Includes two cases of hydrops fetalis.

The autopsied cases in which kernicterus was not present form a heterogeneous group (Table VIII) and deserve individual mention:

In Cases 11 and 25, hydrops fetalis was present. Both babies died on the first day of life.

In Case 22 the infant was born pale and gasping, with mild icterus, and shortly developed petechiae of the face. Death occurred at 4 hours, while transfusion was being attempted. Autopsy disclosed extensive involvement of the brain in petechial hemorrhages. Erythropoiesis in other organs was marked.

In Case 15 the baby developed icterus and anemia extremely rapidly after birth, with marked enlargement of the liver and spleen. Death occurred at 25 hours. The brain showed the diffuse discoloration already described and pulmonary hemorrhages were present. Two siblings of this infant subsequently recovered from erythroblastosis fetalis of which the outstanding signs were icterus, splenomegaly, and anemia.

Case 29 has been mentioned previously (Miller,[5] Case 8, Table IV). Rh incompatibility was present. The baby was cyanotic at birth and remained so for the duration of life. Blood sugar on the first day was 17 mg. per cent. Jaundice became manifest on the second day shortly before the child died. Death appeared to be due to progressive heart failure. At autopsy the liver was large, the spleen of normal size. Erythropoiesis was moderately increased in the liver. There was eosinophilia in the pars anterior of an enlarged pituitary gland, increased glycogen in the heart (1.6 per cent), and generalized splanchnomegaly. No anti-Rh substance was detected in the mother's serum. The mother developed diabetes mellitus about a year after the termination of this pregnancy. These circumstances make it seem very doubtful that death was due to erythroblastosis fetalis.

Case 41 was that of a premature infant (birth weight 2,250 Gm.) in whom icterus was first noted on the fifth day, although it may have been present earlier. The baby received clyses of saline after the second day in accordance with the usual standards for the management of premature infants on our service. Weight gain was rapid, and on the tenth day massive edema was apparent. Death occurred on the twelfth day apparently from heart failure. At autopsy the liver and spleen were of normal size, without any increase in erythropoiesis. The brain was normal. There was marked cardiac hypertrophy (32 grams). Although Rh incompatibility was demonstrated, no antibody was found in the mother's serum, and furthermore the infant was the result of the first pregnancy of a mother who had had no previous transfusion. These considerations seriously challenge the diagnosis of erythroblastosis fetalis.

(Cases 29 and 41 will not be further considered and do not appear in any of the tables, since the diagnosis of erythroblastosis fetalis is in doubt.)

In Case 39 death occurred on the twentieth day of life shortly after transfer from a neighboring community and before therapy could be initiated. The red blood cell count on entry was 600,000 cells per cubic millimeter. A sibling later recovered from erythroblastosis fetalis following transfusion.

In Case 7 (birth weight 1,700 Gm.) icterus developed on the first day and then anemia appeared, for which transfusion was necessary. Death occurred at 1 month from hydrocephalus complicating subdural hematoma. The only residual at post-mortem of the acute erythroblastosis fetalis was a large liver with periportal fibrosis (Miller's[5] Case 12, Table IV).

In four cases permission for autopsy was not granted. In Case 4, which has been discussed in detail by Miller[6] (Case 4), the diagnosis of kernicterus is certain on clinical grounds. In Case 34 death occurred suddenly on the fourteenth day, and appeared to follow the aspiration of vomitus. A sibling of this baby later died of kernicterus (Case 74). In Cases 52 and 63 death was very sudden, in both instances on the second day. Case 52 resembled Case 22 in certain of the clinical manifestations (anemia, petechiae).

If we exclude from consideration those cases where death was avoidable (Case 39) or we were reasonably certain not due to acute erythroblastosis fetalis (Cases 7, 29, and 41), it is seen that an unfavorable outcome (death or survival with mental retardation) has been associated with kernicterus in 20

of 27 cases in this series. This high incidence of kernicterus is in accord with recently reported[3] observations elsewhere. In attempting to gain insight into the mechanism of occurrence of this important complication of erythroblastosis fetalis we have tried to correlate kernicterus with the other findings of the disease.

CLINICOPATHOLOGIC CONSIDERATIONS

It has been recognized[4] that lack of red cells is rarely the cause of death in erythroblastosis fetalis. In the babies who developed kernicterus in this series the minimum red blood cell count was above 1.8 million in all, and above 3.0 million in many for the duration of the illness. These patients showed no greater tendency to develop anemia than the group that recovered and in several of the cases of kernicterus anemia was conspicuous only by its relative absence. More noteworthy than the lack of anemia in many of these babies with cerebral involvement, however, was the comparative lack of signs of hematological distress. The size of the spleen may be taken as measuring roughly the demands placed upon the organ in removal of products of red blood cell destruction.[7] It is commonly described in units of fingerbreadths in the living infant. About one-quarter (10) of the surviving cases (43) in this

TABLE II. DETAILS OF CLINICAL AND ANATOMIC FINDINGS IN AUTOPSIED CASES

CASE	ICTERUS	BODY WT. (GM.)	HEART (GM.)	LIVER (GM.)	SPLEEN (GM.)	FINGER-BREADTH	EXTRA-MEDULLARY ERYTHRO-POIESIS
A. Cases with kernicterus							
1	2nd day	3,200	30	150	14	1	Slight
5	1st day	2,095	16	110	28	2	Marked
9	3rd day	3,155	35	140	25	2	Slight
33	Birth	3,100	20	140	22	2	Moderate
47	1st day	3,360	18	145	23	2	Normal
48	1st day	3,940	21	190	23	1	Slight
56	1st day	2,410	22	85	10	1	Slight
64	Birth	2,600	17	120	8	1	Slight
74	Birth	2,650	23	180	26	1	Marked
65	1st day	3,575	27	150	27	2	Slight
2	3rd day	2,975	24.5	100	13	1	Slight
75	1st day	2,675	15	110	11	1	Slight
73	1st day	3,800	22	200	32	2	Moderate
B. Cases without kernicterus							
11	Birth					?0	Marked
15	3 hours	4,304	35	338	45	3	Marked
22	Birth	3,147	22	203	25	2	Marked
25	Birth	4,700	60	320	47	3	Marked
C. Probably not erythroblastosis fetalis							
29	1st day	4,725	50	260	12	0	Moderate
41	4th day	2,715	32	100	6	1	Normal

series had spleens recorded as being 3 or more fingerbreadths enlarged. Yet in eleven of twenty babies who developed kernicterus the maximum recorded size of the spleen was 1 fingerbreadth or less and in none of the remainder was the maximum measurement as much as 3 fingerbreaths. Nor is the weight of the organ necessarily outstanding at autopsy, as shown in Table II, where reasonably satisfactory correlation is seen between the weight of the spleen

post mortem and the size in fingerbreadths before death. These striking figures reflect only in part a slight tendency of kernicterus to occur in the smaller infants. The weight range, 3,000 to 4,000 Gm., includes eleven cases of kernicterus and the majority of surviving infants who had 3 fingerbreadths' enlargement of the spleen; both groups are fairly evenly distributed. Table III shows that the probability that no infant in this weight range with kernicterus would be in the group with 3 fingerbreaths enlargement is P less than 0.10. Five of the infants with kernicterus had only a 1 fingerbreadth enlargement. These figures suggest not only that kernicterus is not necessarily associated with marked blood destruction, but also that blood destruction may be generally less in the babies with kernicterus than in an equally large group of *recovered* cases of erythroblastosis fetalis.

TABLE III. RELATION OF SIZE OF SPLEEN TO OUTCOME IN WEIGHT RANGE 3,000-4,000 GM.

	SPLEEN			
	1 FINGER-BREADTH OR LESS	2 FINGER-BREADTHS	3 FINGER-BREADTHS OR MORE	AVERAGE WEIGHT
Kernicterus (11 cases)	5	6	0	3,543 ± 191 Gm.
Recovered (29 cases)	15	5	9*	3,427 ± 261 Gm.
Total	20	11	9	
Kernicterus expected	5.5	3.0	2.5	$X^2 = 5.5$ $P < 0.10$

*Weight range 3,000-3,995 Gm. Average weight 3,458 ±316 Gm.

Extramedullary erythropoiesis is a second index of the reaction of the hematopoietic system to injury. Taking the liver as a representative organ, we observed considerable variation in erythropoiesis in the cases with kernicterus (Table III). The majority showed only minimal increases. In the few autopsied cases in which kernicterus was not found, erythropoiesis was generally much more marked. There is some hint that the most marked extramedullary erythropoiesis was likely to be seen in the infants in whom icterus was present at birth or developed very soon thereafter.

However, the time of onset of icterus seems to have no prognostic significance in this series. As shown in Table IV neither the outcome in general nor the incidence of kernicterus is related to the time of onset of jaundice, whether before birth, during the first twenty-four hours, or later. Nor were we able to relate the occurrence of kernicterus to the intensity of icterus. Many extremely jaundiced babies recovered completely, whereas certain infants with mild or only moderate degrees of icterus developed kernicterus.

TABLE IV. RELATION OF OUTCOME IN ERYTHROBLASTOSIS FETALIS TO TIME OF ONSET OF ICTERUS

	ICTERUS			
	AT BIRTH	IN LESS THAN 24 HR.	IN MORE THAN 24 HR.	NEVER
Total	25 cases	24 cases	17 cases	6 cases
Recovered	17	9	12	5
Dead	8 (32%)	15 (62%)	5 (29%)	1
Kernicterus (%)	5 (20%)	10 (42%)	5 (29%)	0

TABLE V. RELATION OF KERNICTERUS TO THE OCCURRENCE OF EDEMA

TIME OF ONSET	BIRTH WEIGHT (GM.)	TIME OF ONSET	BIRTH WEIGHT (GM.)
Recovered patients (43 cases)		*Cases with kernicterus (20 cases)*	
2nd day	4,500	2nd day	2,055 (Case 5)
3 hours	4,125	Birth	3,100 (Case 33)
Birth	3,610	4th day	3,575 (Case 47)
Birth	4,650	5th day	2,360 (Case 56)
1st day	3,600	5th day	3,200 (Case 65)
3rd day	3,600	1st day	3,800 (Case 73)

Edema was about twice as common in the cases developing kernicterus as in the group of recovered cases and was mild in both groups (Table V). In four of six patients with kernicterus, edema did not appear until within twenty-four hours of death, whereas, in four of the six edematous patients who recovered, the edema was established by the end of the first day.

We found kernicterus somewhat more likely to occur in the smaller babies. Table VI, which relates birth weight to the occurrence of kernicterus or survival, shows that a birth weight of 3,000 Gm. divides the group with kernicterus into 50 percentile partitions and the group of recovered patients into 25 and 75 percentile partitions. This result has no statistical significance ($P < 0.20$); but it is noteworthy that of the babies who developed edema as a manifestation of acute erythroblastosis fetalis and recovered, all weighed 3,600 Gm. or more at birth (Table V), while of those edematous babies developing kernicterus, only one weighed more than 3,600 Gm. (Case 73).

In no case of kernicterus was there anatomic evidence of such blocking of terminal blood capillaries with cellular debris as Diamond and Denton[7] and Liber[8] suggest may contribute to an unfavorable outcome in erythroblastosis fetalis. In Case 22 and in the stillborn hydropic sibling of one of our patients who recovered, on the other hand, there was a diffuse petechial hemorrhagic injury to the brain with evidence of attempted repair, which might be interpreted as resulting from the plugging of small blood vessels by masses of nucleated red blood cells, which were present in abundance and were larger than the normal cell. In neither of these cases was kernicterus seen, whereas in certain of the brains in which kernicterus was intense in gross sections, no microscopic abnormality whatever was encountered. Necrobiosis and other changes described elsewhere[3] as characteristic of kernicterus were absent, as well as any evidence of vascular injury.

TABLE VI. RELATION OF OCCURRENCE OF KERNICTERUS TO BIRTH WEIGHT

	BIRTH WEIGHT				
	BELOW 2,500 GM.	2,500 TO 3,500 GM.	ABOVE 3,500 GM.	BELOW 3,000 GM.	ABOVE 3,000 GM.
Kernicterus	4	8	8	9	11
Living	3	25	15	11	32

Except for the replacement of red blood cells in infants where anemia was a real threat to life, the use of blood transfusion in therapy of erythroblastosis fetalis has not appeared to affect the outcome, as shown in Table VII.

TABLE VII. RELATION OF TRANSFUSION TO OUTCOME IN ERYTHROBLASTOSIS FETALIS

DONOR	TRANSFUSED WITHIN FIRST FIVE DAYS OF LIFE			TRANSFUSED FIRST DAY		
	LIVING	DEAD	KERNICTERUS	LIVING	DEAD	KERNICTERUS
Father	4	3	2	2	1*	0
Untyped	12	4	3	3	1†	0
Rh negative	10	5	4	2	4	3

*Case 15.
†Case 25.
Three cases of kernicterus were transfused only when moribund, one with untyped, and two with Rh negative blood; they are excluded from consideration.

Consideration is limited to transfusions given during the first five days of life, since it is within that period that the great majority of deaths from acute erythroblastosis fetalis occur (Table VIII). No significant or striking correlation of outcome with the Rh type of the blood used nor time of administration was found when this five-day period or shorter periods were considered, until the effect of transfusions given within the first day was noted. It is seen that no infant who received Rh-positive blood on the first day of life died with kernicterus. This suggested superiority of Rh-positive blood given within the first twenty-four hours in preventing kernicterus is by no means statistically significant, but it represents the most striking deviation from the general finding that the type of blood used in therapy had no effect on the outcome.

TABLE VIII. TIME OF DEATH IN ACUTE ERYTHROBLASTOSIS FETALIS

1ST DAY	2ND DAY	3RD DAY	4TH DAY	5TH DAY	LATER
	Case 63				
	Case 52				
	Case 15		K		
Case 22	K	K	K	K	
Case 11	K	K	K	K	Case 34—14 days
Case 25	K	K	K	K	K—8 days

K = kernicterus.

DISCUSSION

Early investigators of the Rh factor were able to demonstrate it only in the red blood cell.[9, 10] It was therefore assumed that the signs and lesions of erythroblastosis fetalis were consequent upon injury to the red cell alone and that hemoclasis was the dominant pathogenetic process.[7, 11] But in infants with kernicterus we have found no uniformly marked anemia, icterus, or other signs of blood destruction, neither clinically nor at post-mortem examination; nor have we found anatomic evidence that blood destruction is involved in the production of kernicterus except as it may lead to an increase in serum bilirubin. Darrow[12] also has been unable to correlate brain damage with severity of clinical signs. Boorman and Dodd,[13] moreover, have recently demonstrated the Rh factor in a variety of tissues, and suggest that prior attempts to demonstrate the factor in body fluids or in aqueous extracts of organs may have been

fruitless because the factor is not very soluble in water. These authors consider it likely that the Rh factor is as general a characteristic of tissues as the A and B factors. It seems plausible that any tissue where Rh specificity is a protoplasmic characteristic should be held susceptible to injury by Rh antibody.

Kernicterus is not yet, however, clearly accounted for in terms of an antigen-antibody reaction. We do not know whether it represents a primary nerve cell injury, with secondary pigmentation and later morphologic change, or whether it is primarily a vascular disease with secondary pigment deposition and nerve cell injury. Vascular endothelial trauma might come from direct assault by the Rh antibody, or from the by-products of intravascular hemolysis. A primary vascular basis for kernicterus is suggested by the fact that the regions in which the pigment is found are those in which asphyxia and anoxia generally have their most devastating effects.[14, 15] This has been considered the probable result of the fact that these are brain areas which have a relatively poor blood supply,[15] and may therefore be more susceptible to injury when generalized disturbances in blood supply or oxygen transport occur. Edema in erythroblastosis fetalis may well reflect a generalized injury to vascular endothelium, which results in increased capillary permeability when tissue anoxia occurs. The high incidence of kernicterus in smaller babies with edema suggests that edema and kernicterus may be etiologically related.

In experimental studies relating to the blood-brain barrier Broman[16] concluded that vascular injury was prerequisite to staining of injured cerebral tissue by trypan blue, which bilirubin is said[17] to resemble in its behavior toward the cerebral vascular endothelium. Broman felt that nerve cell injury alone did not give rise to altered reactivity to trypan blue. King,[18] on the other hand, holds brain tissue injury essential to this altered reactivity, and suggests that vascular changes may follow nerve tissue injury in a manner analogous to the chemotactic phenomena of inflammation. Certain antibodies[17] are known to diffuse readily across the hematoencephalic barrier, and in the event that brain cells are shown to be Rh positive, then injury of such cells by Rh antibody becomes a readily conceivable possibility.

Immaturity of cerebral or cerebrovascular tissues may play an etiological role in kernicterus, as suggested by Table VI. There is experimental confirmation of this notion. Friedemann[17] found that certain substances permeated the cerebral vascular endothelium of young mice which did not cross the endothelium of older animals. Frohlich and Mirsky[19] produced convulsions in young rats by the administration of bilirubin, but not in older rats. We and others[20] have observed kernicterus in premature infants, with and without sepsis, where the role of isoimmunization could be reasonably excluded. However, almost one-half (8) of our patients with kernicterus weighed over 3,500 Gm. at birth, which hardly suggests immaturity. Moreover, in a recent review of kernicterus, Docter[3] concluded that, except where erythroblastosis fetalis was also present, kernicterus has never been seen complicating congenital atresia of the bile ducts, which is the principal condition besides erythroblastosis fetalis which may produce intense jaundice in the newborn

period. While immaturity may well play some part in the causation of kernicterus, we feel that it does not by any means play the dominant role.

Even if kernicterus proves to be the result of local injury to Rh-positive tissues by anti-Rh substance, there is no explanation for the fact that the infants' Rh-positive red blood cells do not protect the brain from this local injury, nor any accounting of the possibility that in infants with kernicterus blood destruction may be moderated in comparison with a large group of recovered cases. It may happen in certain infants with erythroblastosis fetalis that the red cells have diminished capacity to absorb Rh antibody, that the red cells are resistant to destruction by antibody, or that the antibody has an equal or greater attraction for other tissues. Macklin[21] has proposed that in certain instances sensitization of the mother may be initiated by red cells with an Rh-antigenic structure characteristic of an earlier stage in the development of the fetal red cell than is represented by the fetal cell at term or the adult red cell. Antibody resulting from contact with such cells might have a great affinity for fetal tissues other than the erythrocyte. Alternative speculations are that ante-partum exposure of fetal erythropoietic tissues to small quantities of anti-Rh substance might so alter the mechanism for elaboration of Rh factor that certain erythrocytes at term are unreactive to maternal antibody, or that fetal placental tissue itself, with an Rh-antigenic structure more or less complex than that of the red blood cell, may in certain cases alter the specificity of maternal sensitization.

The possible role of "blocking antibody" in moderating blood destruction in infants with kernicterus is not clear at the present time. Wiener[22] reports that the presence of such antibody may give a false Rh-negative result in the typing of certain erythroblastotic infants and also confuse the picture of Rh sensitization in the mother when special tests[23] are not done. It is conceivable that "blocking" of fetal cells might turn the usual type of antibody to other tissues. However, in Case 56 of our series careful tests for blocking antibody were done, and none reported, while the titer of ordinary antibody was 1:16. The pathologic signs of blood destruction were minimal in this infant (Table II), and this was true of the clinical signs as well (icterus index 40, no normoblastemia, hemoglobin 9 Gm.). Kernicterus was marked in gross sections, but no microscopic abnormality was discovered in the brain. This case makes it appear that the presence of blocking antibody is not essential to any sparing of signs of blood destruction in an infant with kernicterus.

The common delay after birth in development of signs of erythroblastosis fetalis suggests that factors associated with delivery may be of great importance in the study of the disease. The fact that kernicterus is very common in infants who develop icterus only after birth and the fact that certain of the infants dying of kernicterus have little or no sign of long-standing injury due to maternal antibody suggest further that these factors associated with delivery may be of such significance as to account for kernicterus in some babies. It should be emphasized that these factors may also give rise to an illness in which blood destruction is marked and recovery takes place notwithstanding.

This hemoclastic type of erythroblastosis fetalis, as indicated by the size of the spleen, bears no more relation to the time of onset of icterus than does kernicterus.

It is well known that the act of delivery of an erythroblastotic infant has a very significant effect on the mother, since her production of antibody is stimulated at this time, and her titer of antibody becomes higher in the weeks post partum than it was before delivery.[24] It seems likely[25] that this increase in maternal antibody titer after delivery is due to stresses placed upon the placental barrier during labor which result in the entrance of fetal blood cells, with or without placental tissue, into the maternal circulatory system. The period of the second and early third stages of labor, which require that the placenta adjust to decreasing uterine volume and surface, may be a critical period in determining the amount of fetal antigen to which the mother is exposed. It is not unreasonable to suppose that if fetal cells can reach the maternal circulation during this period, then maternal serum may by a similar process attain the fetal blood stream. If such intrapartum transfer of antibody from mother to fetus dominates the development of erythroblastosis fetalis in a given infant, then a delay of several hours after delivery in development of signs of the disease would be understood. If kernicterus were the outcome, a paucity of signs of long-term injury to fetal tissues (such as organ hypertrophy or marked erythropoiesis) might likewise be accounted for.

While such speculative considerations as these may explain the occurrence of erythroblastosis fetalis in an infant who appears normal at birth, they do not help us to understand why preferential blood destruction does not protect babies with kernicterus. A further explanation in terms of antigen-antibody reactivity or other factors is necessary. It is conceivable that the rate of delivery of antibody from mother to fetus might play some role, the more rapid rate allowing general distribution of antibody to fetal tissues before the action of the Rh-positive erythrocyte in sparing tissue damage might become effective. Our data on the course of labor do not permit us to examine this possibility, nor is there certainty that factors determining the amount and rate of any intrapartum transfer of antibody will be capable of evaluation.

If future studies or experimental work confirm the suggestion that intrapartum transfer of antibody plays an important role in the development of erythroblastosis fetalis in the infant, it might be found that the transfer of antibody from mother to fetus could be minimized if delivery were accomplished by cesarean section, with rapid securing and ligation of the umbilical cord. Even when pelvic delivery is rapidly effected, there may be placental stresses during the second and early third stages of labor which hold an unpredictable hazard for the infant.

Diamond[20] reports that the obstetrical management of mothers with erythroblastotic babies has already significantly lowered the mortality among the infants. He advises early interruption of pregnancy in the event of a rising anti-Rh titer, as soon as there is a viable fetus for whom mild erythroblastosis fetalis superimposed upon prematurity should not prove too great a burden.

Our experience with the relation of kernicterus to the smaller infants suggests that this program has limitations. It may be that some increased factor of safety would accrue if cesarean section were used in effecting the early delivery.

Another possible conclusion based on the foregoing speculations is that early use of Rh-positive blood transfusion might ameliorate the prospects of an infant in whom kernicterus is anticipated by offering a sponge to antibody transferred during delivery. It would be hoped that fresh Rh-positive cells (of appropriate subtype), not exposed to maternal antibody at any time during their development, would have a high affinity for maternal antibody, sparing tissue cells from injury. If the transfused cells had no greater affinity for maternal antibody than the fetal cells, or if they were of no value in fixing circulating antibody, then their use in therapy would be worthless as far as altering the prospect of kernicterus is concerned. But Mollison[26] and others[27] have shown that, even later in erythroblastosis fetalis than the first few hours after birth, Rh-positive cells used in treatment are more rapidly destroyed than Rh-negative cells. The implied continuing presence of available antibody in the infant leads us to consider that *in certain infants* the destruction of transfused Rh-positive cells may be a desirable event, causing the removal of anti-Rh substance from fetal fluids and possibly from loose attachment to fetal tissues. Rh-negative blood is undoubtedly advantageous in the treatment of uncomplicated erythroblastotic anemia[27] or in the treatment of the infant, rare in our experience, in whom blood destruction itself seems to be the main threat to life. But we do not feel that its routine use in the therapy of erythroblastosis fetalis will necessarily lower the incidence of kernicterus, since our results indicate that kernicterus is more likely the result of direct injury to cerebral or cerebrovascular tissues by antibody than the consequence of blood cell destruction.

It cannot be too strongly emphasized that while the conclusion that kernicterus may not be the result of blood destruction seems justified by the observed facts, on the other hand, suggestions as to how kernicterus might be prevented are theoretical, and neither proved nor rigorously tested. Analysis of other large series of cases of erythroblastosis fetalis must be made, testing the reliability of our data before any commitment regarding therapy can be formulated. Our experience, and that of others[12, 28] who have employed early transfusion of Rh-positive blood, suggests that it is not generally harmful to the infants in whom it is used. It may be that only further use can answer the question whether the foregoing theoretical considerations have any basis in fact or any practical application. Diamond[29] would caution very strongly against the use of Rh-positive blood in infants in whom cells sensitized by the so-called blocking antibody may be present. He has found that even *washed* Rh-positive cells may agglutinate in the presence of Rh-positive cells sensitized by blocking antibody. This reaction has been seen in vitro, and appears to have been the reason for an unfavorable outcome in at least one case of erythroblastosis fetalis in Diamond's experience. It may be pointed out that if it were possible to obtain an Rh-positive antigen unattached to the red blood cell, this

substance would be preferred to Rh-positive blood as a therapeutic agent since it might neutralize antibody without enhancing hemagglutination or hemolysis.

SUMMARY

In a series of seventy-two cases of erythroblastosis fetalis there were twenty-five deaths with twenty-one autopsies. Four of the surviving patients have mental retardation. An unfavorable outcome was associated with the clinical or pathologic signs of kernicterus in twenty cases. In twelve cases of kernicterus there were also focal pulmonary hemorrhages and these infants displayed a striking clinical picture, made up variously of drowsiness, spasticity, opisthotonos, signs of motor irritability, respiratory irregularity, pulmonary râles and rhonchi, and bloody discharge from the upper respiratory tract.

Clinical and pathologic features of the cases with kernicterus suggest that blood destruction is not the primary determinant of nuclear damage. The possible roles of immaturity, vascular injury, altered antigen-antibody reactivity, and intrapartum transfer of antibody in the pathogenesis of kernicterus are discussed.

I wish to express my appréciation to Dr. Louis K. Diamond for the performance of many blood tests in this series of patients and for his criticism of this paper.

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THE IMPORTANCE OF CHRONOLOGIC RECORDS IN THE MANAGEMENT OF ALLERGIC CHILDREN

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THE importance of accurate histories in the diagnosis and treatment of allergic diseases has been repeatedly emphasized. Stevens pertinently remarks that "An hour's time spent in taking a history is worth more than a hundred skin tests." Once obtained, the items in the history cannot be regarded with the finality of fixed statistical data, but as clues that may need rechecking. The skillful allergist learns to sift the chaff from the wheat in the patient's story long before the skin has been scratched. He has no way, however, of proving or disproving the truth of related episodes, and as every pediatrist who has had to fill out a college entrance blank for one of his wards knows, the authenticity of history recitals from the mother varies inversely with the length of time elapsed and the size of her family. The average history recorded by the fledgling clinical clerk is a gallimaufry of distracted parental memories.

In the field of allergic diagnosis, more perhaps than in other fields of medical diagnosis, chronologic relationships assume great importance. An asthma attack "about six months ago" has little specific significance. Asthma spells occurring from March through October at least point a finger to a possible mold allergy relationship. Rackeman illustrates the importance of the chronologic relations by the story of the schoolboy who had attacks three times a year—"eleven months ago, seven months ago, and five months ago"—a meaningless story until the dates were recorded and it was appreciated that December 21, March 28, and June 12 represented the change from boarding school to a home where there was a cat.

The intimate parent-physician relationship enjoyed by the pediatrician permits him to obtain details missed or confused in a clinical biography written long after their occurrence and the mother of a child, if instructed, will willingly phone the physician's office to report medical incidents at the time of their occurrence. The record of these details may be incorporated on a chronologic sheet in the patient's folder by the physician's secretary or nurse at that time. The mother is much less apt to keep a dependable diary. As the physician adds the details of his house or office calls, a chronologic record is obtained which, on one sheet, will give a graphic visualization of a child's entire medical history.

By the use of arbitrary symbols to express various symptoms or symptom-complexes the secretarial work involved is reduced to a minimum. Symbols are used to express these signs and symptoms: upper respiratory infection, excessive sneezing, hay fever, ambulant asthma, asthma severe enough to con-

fine patient to bed, atopic dermatitis, nonallergic skin disease, styes, digestive upset suggesting allergic component (colic), vomiting, diarrhea, digestive upset of infectious type, nosebleed, enuresis, vaginitis. (No originality is claimed for the characters of symbols used, and many persons with greater artistry or ingenuity may find a more graphic medical shorthand.)

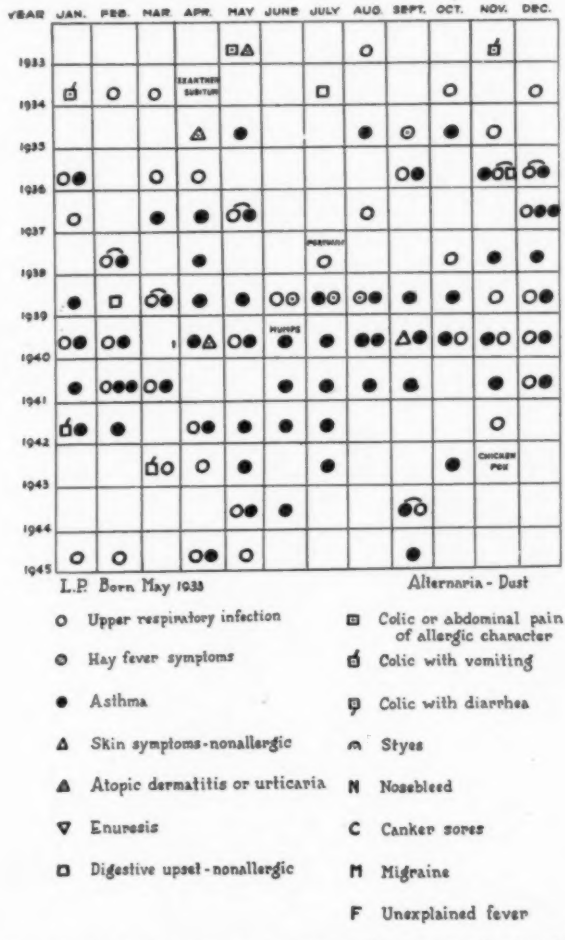

Fig. 1.—Chronologic chart. The year-round incidence of allergic signs is noted in third year of life. The reduced incidence of asthma during the last five years is graphically presented.

By the use of these symbols on a page lined vertically by months, horizontally by years, a ten-year listing of medical incidents may be portrayed on a single page (Fig. 1). Such a chronologic record will, at a glance, show in what months the child's symptoms appear, the frequency of attacks, what sys-

tems are involved, change of shock organ bearing the brunt of allergic attack. Records of this character have frequently shown discrepancies between the family's recollections and the actual incidence of certain symptoms. They refute or confirm the impressions of the effectiveness of methods of treatment.

In the cases of pediatric patients later referred to an allergist who treats adults, transfer of the chronologic records will be of help to the allergist and patient alike and provide a more accurate background for guidance and therapy.

NONRACHITIC BOWLEGS IN CHILDHOOD

Osteochondrosis Deformans Tibiae

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IT SEEMS likely that many medical men will continue to consider the childhood condition of bowlegs as almost invariably the result of rickets. They will, therefore, continue to explain the cases in which bowlegs have developed in spite of regular, adequate doses of vitamin D by the unconvincing arguments that assimilation has been faulty or that individual requirements have been excessive. This, as an initial conclusion, should not be accepted by the pediatrician or the orthopedic surgeon until the differential points have been visualized by x-ray. Perhaps the reassertion that the occurrence of nonrachitic bowlegs is surprisingly frequent will serve to emphasize an alternate diagnosis until the syndrome of *osteochondrosis deformans tibiae* or "tibia vara"[3] will also come to mind whenever a case of bowlegs is encountered. Probably very little harm has been done in the past by the assumption that bowlegs always means rickets. Giving more and more cod liver oil in misdirected treatment of nonrachitic bowlegs has certainly caused no injury and the final correction of the deformity can be expected to become an orthopedic procedure in any case. Recognition of the nonrachitic nature of bowlegs would, however, relieve the attending physician, or his predecessor, of the blame for failing to control the advance of rickets which has been rightly classed as a preventable disorder.

The entity *tibia vara* seems to have been first effectively publicized by Blount[3] who made an analysis of the condition in sufficient detail to establish diagnostic features distinguishing it from rickets, dyschondroplasia (Ollier's disease), syphilis, tuberculosis, osteochondritis. The conception of the condition has been further advanced by the observations of Barber[1, 2] and the *infantile* and *adolescent* types of this disorder further described. The adolescent type seems to be a later, fixed stage of the deformities of the infant type but can be properly recognized as such with the aid of the history. Because of the maturity of the bones at the time it is usually recognized, the correction of adolescent bowlegs can be accomplished only by some radical surgical procedure. The infantile type of nonrachitic bowlegs, on the other hand, can be recognized early when the bones are still plastic enough to permit successful, nonsurgical treatment. A plan for this treatment is to be herewith presented as a routine which does not necessarily confine the patient to a hospital. It will be clarified by a brief review of the nature of the mechanical problem and a restatement of some observations regarding the response of growing bone to static and active forces.

THE INFANTILE TYPE

A typical example of nonrachitic bowlegs of the infantile type can be diagnosed by x-ray. (Fig. 1.) No better description of the features of this deformity can be found than that presented by Barber[2] and quoted in part: "The bowing is evident as an abrupt angulation with the apex laterally just below the knee. . . . When the deformity occurs in infancy, a bulbous enlargement of the medial tibial condyle is palpable on physical examination and visible in the roentgenograms. This beaklike projection at the metaphysis has been shown to contain islands of cartilage. . . . A general medical examination usually reveals no other abnormalities. There is nothing to suggest rickets or syphilis. . . . Faulty growth of the upper tibial epiphyseal cartilage and delayed ossification of its medial half result in a wedge-shaped deformity of the epiphysis. The lower tibial epiphyseal cartilage occasionally shows similar though less pronounced changes; if this occurs, some lateral bowing just above the ankle may appear. Elsewhere the tibial shaft is perfectly straight. Secondary changes in the medial femoral condyle may augment the deformity."

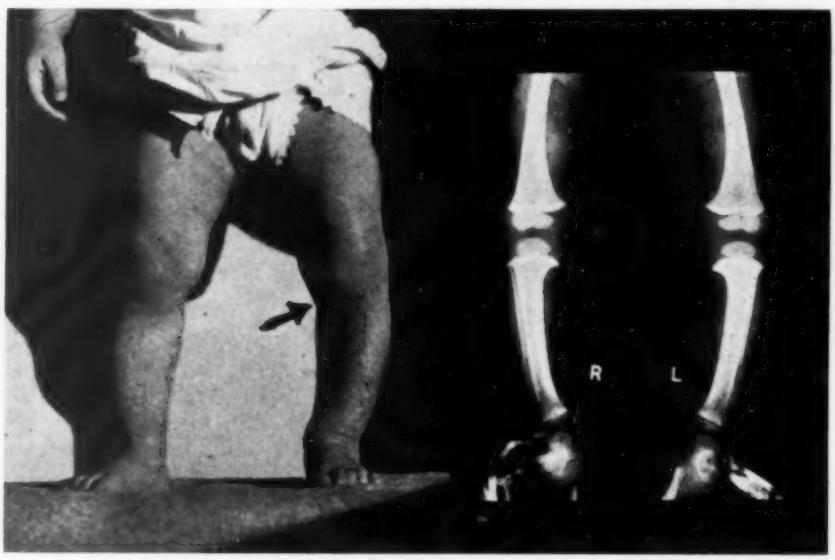

Fig. 1.—Photograph of a case of moderately severe bowlegs. (Case II.) External appearance of the legs gave the clinical diagnosis which was more specifically defined as an example of "tibia vara" upon the evidence of x-ray. Bilateral but differing degrees of bowing were demonstrated with the greatest abnormality in the left leg. Arrow indicates the region of angulation and the x-ray visualizes the characteristic "spur" on the medial side of the upper tibial metaphysis where it had been palpable. The absence of evidence of rickets and the presence of an essentially straight tibial shaft can be emphasized.

An opinion regarding the nature of this localized abnormality of bone growth was expressed by Vargas in the discussion following the paper presented by Barber before the Section on Orthopedic Surgery at the annual session of the American Medical Association in 1942.[2] This opinion was apparently approved

by the author of the paper and the other orthopedic specialists in the group including Blount. Vargas repeated at that time that the occasional occurrence of tibia vara in a patient also having Legg-Perthes' disease, Osgood-Schlatter's disease, or the aseptic tarsal-scaphoid necrosis of Köhler led him to suspect that the unknown causes of these disorders also produced osteochondrosis deformans tibiae. This same idea has been more recently presented as a

Fig. 2.—Patient, age 2 (Case V), in cast after wedging. The first application of plaster had been left undisturbed for five weeks during which time the child had been allowed all activity she could manage, including her favorite position on her back with her legs up on the side of the crib. Bone softening could actually be felt at the end of that time and the usual method of wedging was undertaken (Fig. 3). Typical of the reports of these healthy children is the following quotation from this girl's hospital record: "The patient has shown steady gain in weight . . . from her birth weight of 7 lbs. 6 oz. Feeding during infancy was an evaporated milk formula for five months followed by a cow's milk-water-karo mixture. The patient began cereal in her third month and vegetables in her fourth month. She had 3 to 10 drops of oleum percomorphum each day until about six months ago when cod liver oil was prescribed in treatment of the bowlegs which were first noted at that time."

definite fact in an authoritative work by Caffey[4] in which the x-ray diagnosis of all of these conditions is discussed under the single heading of "Focal aseptic necrosis" and local eschemia is mentioned as the common pathogenic mechanism. Regardless of the etiology, it can be considered an exaggeration of a physiologic deformity and, with or without treatment, expected to undergo

spontaneous progression or regression under the influence of unknown causes including the hypothetical activating effect of local trauma.

DIFFERENTIAL DIAGNOSIS

With the features of this condition in mind, it should not be difficult to distinguish the infantile type of tibia vara from the two other conditions it most closely resembles: rickets and dyschondroplasia (Ollier's disease).

TABLE OF DIFFERENTIAL DATA

	TIBIA VARA (INFANTILE TYPE)	RICKETS	DYSCHONDROPLASIA (OLLIER'S DISEASE)
Age at onset	Second or third year	First year	Congenital
General health	Excellent	Poor: fever, weight loss, sweating, and other bone changes	Poor
Bowlegs	Bilateral but different; only objective sign	Bilateral; late in the disease	Unilateral or several bones involved besides tibia
Epiphysis	Ossification delayed in medial half	Broadened; symmetrical ossification but mottled	Irregular ossification near epiphyseal line
Epiphyseal line	Normal	Widened and vague	Broadened and vague
Metaphysis	Medial "beak" and angulation causing the bowed leg; light areas	Widened with irregular flare; calcification poor	Mottled by irregular masses of cartilage
Shaft of tibia	Straight and normal in density	Bowed with calcification poor	Bowed with irregular masses of cartilage

TREATMENT

Since spontaneous improvement of the deformity on one or both sides has been known to occur in the milder forms of the infantile type of osteochondrosis deformans tibiae and since recurrence has also been observed when surgical correction has been undertaken before the process has become static, an attempt to treat the existing deformity by nonsurgical means is not only justified but is definitely preferable. It is assumed, of course, that the mere fact that the bowing is obvious to the child's parents gives the needed indication for treatment of some sort. As has been remarked, the immature bone in these cases of infantile nonrachitic bowlegs provides a plastic medium for the orthopedic surgeon to mold into correct alignment. Another point, previously suggested, is the fact that the abnormal bone growth process, which is not itself being treated, remains active so that the mechanically effective measures for correction must be continued until the process has become static or there will be a recurrence. In treatment it will be found expedient to use the bone softening effect of inactivity and the bone hardening effect of weight bearing to the best advantage at chosen moments. From these ideas can be constructed a plan for rational, non-surgical treatment in three stages.

1. *Immobilization Until Bone Softening Has Taken Place.*—This can be effectively accomplished in plaster casts. When applying these it is borne in mind that the tibia (near the knee) is the bone involved in the abnormal angulation and that the femur is not usually distorted. It is also evident that if the cast is

applied to make the bones soften from lack of use, any weight bearing while in the cast will defeat the plan to produce bone atrophy. As a consequence, the plaster is carried from the patient's foot to the upper thigh on each side leaving the hip joints free. The two leg casts are then rigidly joined together by a cross bar which keeps the legs in abduction to facilitate nursing care and make it impossible for the patient to stand. (Fig. 2.) The casts are made heavy enough to anchor the child to minimal activity and firm enough to stand the leverage of subsequent wedging. Added bulk is, incidentally, due to felt pads beneath the plaster in anticipation of the pressure to be exerted when wedging starts. In this restraint the bones become palpably flexible in from six to eight weeks.

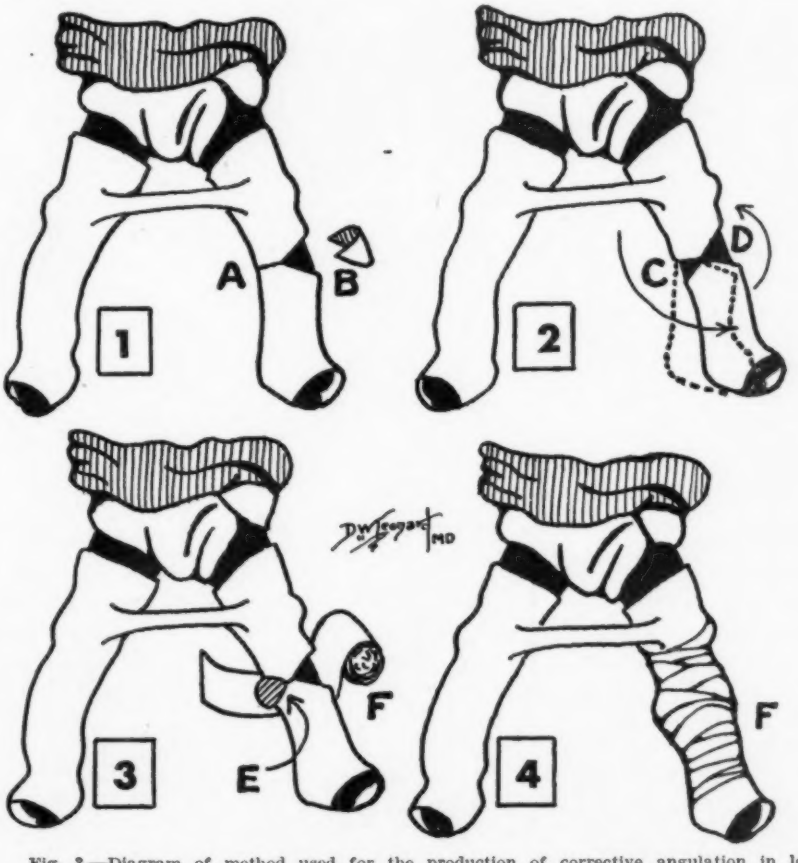

Fig. 3.—Diagram of method used for the production of corrective angulation in leg casts. Cuts through the plaster are made around the cast at the level chosen (A-B) so that an elliptical piece can be removed from the *outside* (B). The degree of bending that the softened bone will stand must be judged by experience and may often be nearly enough to close the opening made on the outside of the cast and open a similar one on the inside (C). The latter is then filled with a mass of wadded plaster bandage (E) and the area welded together with several circular turns (F).

2. *Gradual Correction of the Bowing.*—This is undertaken by physical force when it is possible to rely on the advantage of softened bones. This is accomplished by cutting the plaster near the point of tibial angulation, forcibly correcting the abnormal angle to a degree determined by conservative judgment at the time of the manipulation and then replacing the plaster. (Fig. 3.) It is expected that this step may be repeated at two- or three-week intervals as many times as is necessary and that a new cast will be applied whenever the limit of practical wedging has been reached by the old one. Progress at any point may be checked by superimposing x-rays or by measurements on superimposed tracings. (Fig. 4.)

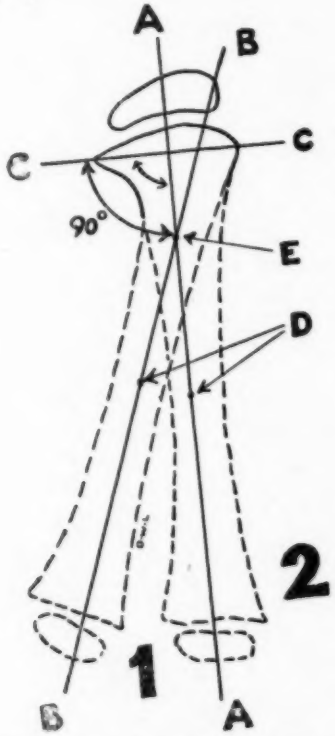

Fig. 4.—Measurement of the degree of correction made on superimposed x-ray tracings (1 and 2). The tracings are each marked with lines (*C-C*) which connect the medial and lateral points of the metaphysis of the tibia and are then superimposed so that these lines coincide. The parts of the bones distal to that line will then lie in a position determined by the degree of correction obtained. If a geometric evaluation is desired, it is suggested that lines (*A-A*, *B-B*) be drawn in each tracing to represent the axis of the shaft passing through its midpoint (*D*). These axis lines in the superimposed tracings will cross each other at the pivotal point of the corrective bending (*E*) and will also cross the lines *C-C*. Several angles can be measured but when the angle between *C-C* and *A-A* approaches a right angle the stage of theoretically perfect correction will be reached.

3. *Maintaining position.*—The final and longest stage of treatment is the maintaining of position and walking until the bones have hardened with use and the original process has become static. When satisfactory correction has been

obtained by repeated wedging and has been checked by x-ray, the casts may be discarded in favor of a pair of ambulatory braces. These braces are of the usual type and designed to exert some force in order to continue the process of correction but they are primarily intended for protection against recurrence of the

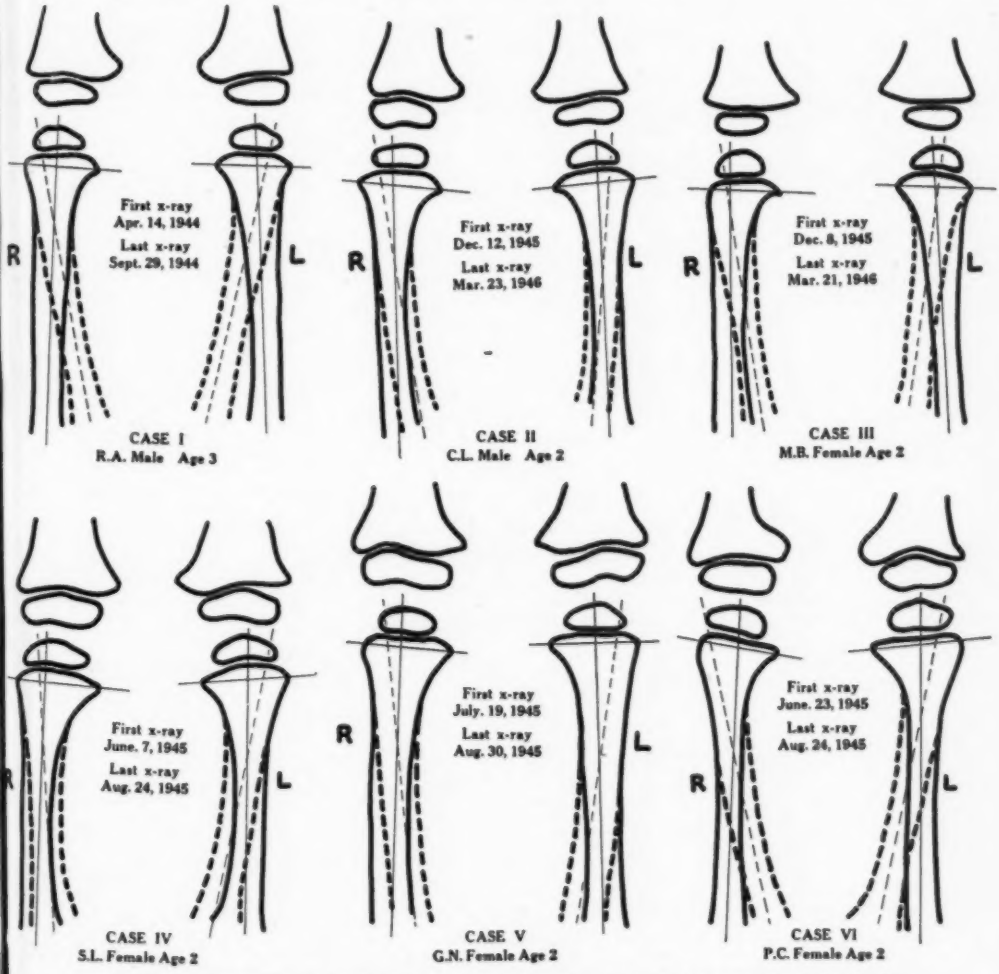

Fig. 5.—Photographic reductions of actual superimposed tracings of the first (broken line) and the last (solid line) x-rays taken during the treatment of six representative examples of tibia vara. Degree of improvement demonstrates that sufficient correction can be obtained by the nonsurgical method suggested.

angulation in the upper tibia. In the absence of special reasons to the contrary the patient would be expected to wear the braces continuously for six months and part of the time for another three months so that the entire duration of the treatment would be approximately one year. Resumption of weight

bearing would be relied on to hasten the hardening of the bone in the new alignment and the period of observation would be expected to make possible an immediate detection of any tendency toward recurrence.

REPORT OF CASES

Following this plan of treatment a number of cases of nonrachitic bowlegs of the infantile type have been treated. As a demonstration of the degree of correction it has been possible to accomplish, superimposed tracings of the first and last x-rays taken in six representative cases are presented. (Fig. 5.) Some of these patients have been hospitalized because of the provisions of the agency authorizing the work; others were cared for at home except for hospital and office calls for the actual work and the taking of x-rays.

SUMMARY

A definite type of nonrachitic bowlegs in childhood has been recalled with clinical and x-ray characteristics consistent enough to justify its classification as an entity under the designation osteochondrosis deformans tibiae or tibia vara. An abnormal angulation at the proximal metaphysis of the tibia is the main feature of this disorder and the cause of the gross deformity recognized as bowlegs. The shaft of the tibia is straight. The true nature of the deformity and its lack of any relationship to rickets can be demonstrated clinically and by x-ray in both the infantile and adolescent types. The first type can be corrected without surgery but the second yields only to radical methods such as osteotomy. A plan of treatment of the infantile type, based on the fact that bones in early childhood are still malleable, has been presented in three stages: (1) immobilization in plaster until the bones have softened, (2) gradual correction of the abnormal angulation by wedging of the casts, and (3) resumption of activity with the protection of braces until the abnormal growth process has become static. It has been pointed out that the plan for nonsurgical treatment of nonrachitic bowlegs, as outlined, makes hospitalization optional.

It has been felt that the relatively frequent occurrence of nonrachitic bowlegs should be emphasized and that the adoption of a practical plan for conservative, nonsurgical treatment of the infantile type should be recommended.

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INFLUENZA VIRUS VACCINE

Local and Systemic Reactions in Children

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IMMUNIZATION of adults with inactive influenza virus has been reported by Hirst, Rickard, and Friedewald.* A mild febrile response and inflammation at the site of injection were noted. However, much more severe reactions have been reported by word of mouth by numerous other people, particularly from members of the Armed Forces. With the lack of any information about dosage or reaction of children to the vaccine, 16 children between the ages of 1 and 8 years were given influenza virus vaccine, types A and B, in variable amounts.† The first four patients were given 0.25 c.c. of the vaccine subcutaneously and the temperature was recorded every 4 hours, for 36 hours or until normal (Table I).

As one patient had a mild local and systemic reaction and another a slight febrile response, six children were given 0.5 c.c. of the vaccine subcutaneously and observed as was the previous group (Table II).

In this group a mild local reaction was noted in every subject and a slight febrile reaction was noted in about one-half of the children. None of the patients appeared extremely ill nor did the local reactions seem much greater than in the previous group. Even though the severity and frequency of reactions seemed somewhat greater than in the group given 0.25 c.c., it was decided to increase the dose to the normal adult dose of 1 c.c. for six patients in a similar age group as was used previously (Table III).

The frequency of the reactions was no greater than either previous group but the severity was markedly increased. All patients had an increase in the local reaction and two of the patients were acutely ill, one having a generalized convulsion at the height of the fever (40.7° C.). Both patients were normal within 48 hours. The two older patients who were given 1 c.c. had no systemic reaction and the local reaction was about the same as in the younger patients.

The observations made in this series of patients showed that the febrile reaction in children is much more frequent than is mentioned in adults. When 1 c.c. was given, the reaction was much too severe to recommend the general use of this amount of vaccine for children. The reaction to 0.5 c.c. of the vaccine is about the same as is noted in adults when 1 c.c. of the vaccine is given. The reaction to 0.5 c.c. of the vaccine is quite mild and we think this dose is optimal and all that will be tolerated for active immunization against types A and B influenza virus. To increase the necessary immunity this dose can be repeated, perhaps, in two weeks.

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*Hirst, G. K., Rickard, E. R., and Friedewald, W. F.: J. Exper. Med. 80: 265, 1944.

†Lederle. This vaccine was supplied through the courtesy of the Lederle Company, New York, N. Y.

TABLE I

SUBJECT	AGE (MO.)	REACTION			
		IMMEDIATE	12 HOURS	24 HOURS	36 HOURS
D. K.	26	Pain	1 cm. nodule; normal temperature	0.5 cm. nodule; normal temperature	Normal temperature
P. W.	21	Pain; 1 cm. erythema	1.5 cm. erythema; s.c. nodule; T. 38.1° C.	1 cm. nodule; normal temperature	0.5 cm. nodule; normal temperature
M. T.	14	Pain	1 cm. nodule; normal temperature	0.5 cm. nodule; normal temperature	Normal temperature
E. A.	13	Pain	1 cm. nodule; normal temperature	0.5 cm. nodule; T. 38.1° C.	Normal temperature

TABLE II

SUBJECT	AGE (MO.)	REACTIONS			
		IMMEDIATE	12 HOURS	24 HOURS	36 HOURS
D. G.	14	Pain	T. 38° C.; 1 cm. s.c. nodule	1 cm. s.c. nodule	T. 38.5° C. 0.5 cm. nodule (normal 60 hr.)
B. H.	32	Pain	1.5 cm. s.c. nodule; normal temperature	1 cm. s.c. nodule; normal temperature	Normal temperature
D. B.	44	Pain	T. 38.6° C.; 0.5 cm. s.c. nodule	Normal temperature	Normal temperature
D. K.	33	Pain	T. 38.1° C.; 1 cm. s.c. nodule	0.5 s.c. nodule; normal temperature	Normal temperature
D. M.	36	Pain	T. 38.4° C.; 1 cm. s.c. nodule	0.5 cm. s.c. nodule; T. 38.6° C.	Normal temperature
D. S.	24	Pain	1 cm. nodule; normal temperature	0.5 cm. nodule; normal temperature	Normal temperature

TABLE III

SUBJECTS	AGE	REACTIONS			
		IMMEDIATE	12 HOURS	24 HOURS	36 HOURS
J. Q.	19 mo.	Pain	1.5 cm. s.c. nodule; normal temperature	0.5 s.c. nodule; normal temperature	Normal temperature
V. P.	30 mo.	Pain	1.5 cm. s.c. nodule; normal temperature	1 cm. s.c. nodule; normal temperature	Normal temperature
C. F.	24 mo.	Pain	2 cm. s.c. nodule; T. 39.6° C.	1 cm. nodule; 1 cm. erythema; T. 37.8° C.	Normal temperature
R. B.	36 mo.	Pain	2 cm. s.c. nodule; 4 cm. erythema; T. 40.7° C.	1.5 cm. nodule; T. 38° C.	0.5 cm. nodule (normal 48 hours); normal temperature
M. L.	8 yr.	Pain	1.5 cm. s.c. nodule; normal temperature	1 cm. s.c. nodule; normal temperature	Normal temperature
P. B.	6 yr.	Pain	2 cm. s.c. nodule; normal temperature	1 cm. s.c. nodule; normal temperature	0.5 cm. s.c. nodule (normal 48 hr.); normal temperature

IMMUNE RESPONSE TO EARLY ADMINISTRATION OF PERTUSSIS VACCINE

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THE prophylactic use of pertussis vaccine has become an accepted pediatric procedure. Pertussis vaccine as an immunizing agent would hardly have attained such widespread favor had clinical trial not justified its value in the prevention and amelioration of pertussis. The combined impressions of so many well-trained and competent clinical observers would seem to weight the scale heavily in favor of the routine use of this immunizing agent, occasional disparaging reports notwithstanding. It is our own experience that whooping cough, in properly vaccinated infants, has been a very infrequent and mild infection. Except for the history of intimate exposure the diagnosis in most instances would have been subject to serious question.

One of the most serious criticisms of pertussis immunization as presently practiced is the fact that we are leaving unprotected the very age group in which the more serious illness and the highest mortality rate occur. Stimson[1] states that in recent years, in many communities, whooping cough has caused more deaths than diphtheria, measles, or scarlet fever, and in children under 2 years of age more than these three diseases combined. Dauer[2] lists the whooping cough deaths by age in the United States during the years 1935 to 1939 thus:

	PER CENT
Under 3 months	40.0
6 to 11 months	24.2
1 year	21.8
2 years	7.1
3 years	3.2
4 years	1.7
5 to 9 years	2.9
10 to 14 years	0.5

As presently done it is the usual custom to administer pertussis vaccine at from 6 to 8 months of age. It has been generally believed that an adequate immune response could not be expected at a younger age in that pertussis vaccine would fail to stimulate adequate antibody response in young infants.

The purpose of this study was to observe the immune response to pertussis vaccine administered to young infants as measured by agglutinin titers at various age levels. We would clearly emphasize that we are not interested in establishing the effectiveness of any particular vaccine or type of vaccine.*

The plan of study was: One-half cubic centimeter of a vaccine containing 40,000 million killed pertussis bacilli (phase I) was administered deep subcutaneously to 129 infants at one week of age, with a second dose of 1 c.c. at

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*The pertussis vaccine used in this study was supplied by Cutter Laboratories, Berkeley, Calif. All agglutination tests were made at the Cutter Laboratories. This courteous cooperation and assistance are gratefully acknowledged.

one month of age, and a third dose of 1 c.c. at 2 months of age. In order to determine the advisability of a booster dose, 1 c.c. of vaccine was administered to 50 previously vaccinated infants at approximately 6 months of age and the agglutinin titer determined one week later. In a smaller group of infants the same dosage and the same interval were employed, the first dose of vaccine being administered at 2 months of age. Agglutinin titers were observed at various age periods as shown in the figure and tables.

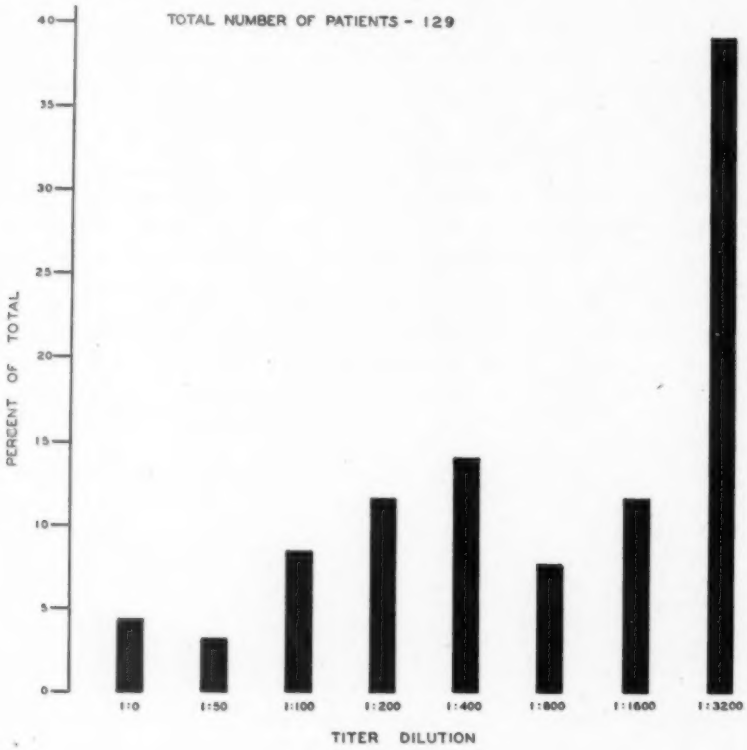

Fig. 1.

It has been shown that some passive transfer of antibodies from the mother to the newborn infant can be expected in some infants born of mothers who have had a previous attack of whooping cough. In order to establish a base line for this study the agglutinin titers of 22 unvaccinated infants one week of age were observed. Table I describes the agglutinin titers in this group of unvaccinated infants.

In 6 infants no transfer of antibodies was demonstrated. In 7 other infants the antibody content as measured by the presence of agglutinins in blood samples would seem inadequate. It would appear that inherited immunity cannot be expected with regularity in newborn infants.

TABLE I

CHART NUMBER	AGE (WK.)	AGGLUTININ TITER	CHART NUMBER	AGE (WK.)	AGGLUTININ TITER
214361	1	1:3,200	214847	1	1:200
214415	1	1:0	214873	1	1:400
214490	1	1:200	214963	1	1:0
214513	1	1:50	214900	1	1:0
214419	1	1:600	214919	1	1:0
214487	1	1:0	214968	1	1:0
214646	1	1:50	215065	1	1:100
214375	1	1:800	215046	1	1:100
214433	1	1:3,200	214187	1	1:400
214737	1	1:400	215143	1	1:200
214733	1	1:400	215176	1	1:200

TABLE II

HOSPITAL NUMBER	2 TO 3 MONTH TITER	4 MONTH TITER	6 TO 7 MONTH TITER	POST-BOOSTER TITER
208889	1:3,200	–	1:3,200	1:3,200
208598	1:400	–	1:3,200	1:3,200
208968	1:50	–	1:50	1:3,200
209036	1:3,200	–	1:3,200	1:3,200
209173	1:3,200	–	1:3,200	1:3,200
209289	1:200	–	1:800	1:3,200
210490	1:400	–	1:400	1:3,200
210515	1:3,200	–	1:400	1:3,200
210014	1:400	–	1:3,200	1:3,200
212100	–	–	1:3,200	1:3,200
208399	1:200	–	1:400	1:3,200
208373	1:200	–	1:50	1:800
208547	1:400	–	1:400	1:800
209268	1:200	–	1:400	1:400
209315	1:100	–	1:3,200	1:1,600
209193	1:400	–	1:3,200	1:800
209265	1:200	–	1:800	1:3,200
208625	–	–	1:1,600	1:800
212243	1:800	–	1:3,200	1:3,200
212289	1:100	–	1:3,200	1:3,200
212755	1:3,200	–	1:3,200	1:3,200
210757	1:0	–	1:3,200	1:3,200
214487	1:400	1:800	1:0	1:50
214646	1:100	1:800	1:3,200	1:3,200
214375	1:400	1:3,200	1:3,200	1:3,200
214433	1:3,200	1:3,200	1:3,200	1:3,200
214733	1:800	1:1,600	1:3,200	1:3,200
214847	1:3,200	1:3,200	1:3,200	1:3,200
214873	1:400	1:400	1:800	1:1,600
214963	1:3,200	1:0	1:0	1:3,200
214900	1:3,200	1:3,200	1:3,200	1:3,200
214919	1:3,200	1:3,200	1:3,200	1:3,200
215176	1:3,200	1:3,200	1:3,200	1:3,200
215174	1:3,200	1:3,200	1:3,200	1:3,200
215748	1:50	1:50	1:100	1:1,600
215242	1:800	1:3,200	1:3,200	1:3,200
215509	1:400	1:800	1:1,600	1:1,600
215665	1:400	1:800	1:1,600	1:1,600
215365	1:200	1:800	1:3,200	1:3,200
215614	1:3,200	1:3,200	1:800	1:800
215448	1:3,200	–	1:1,600	1:1,600
215476	1:800	1:3,200	1:3,200	1:3,200
216495	1:3,200	1:3,200	1:3,200	1:3,200
216596	1:3,200	1:3,200	1:3,200	1:3,200
216785	1:1,600	1:3,200	1:3,200	1:3,200
216167	1:3,200	1:3,200	1:3,200	1:3,200
217164	1:1,600	1:3,200	1:3,200	1:3,200
215667	1:400	1:3,200	1:3,200	1:3,200
216784	1:1,600	1:3,200	1:3,200	1:3,200
216783	1:1,600	1:3,200	1:3,200	1:3,200

The early immune response to pertussis vaccine administered at this early age and measured by agglutinin response is shown in Fig. 1. Blood samples were taken from 129 infants at 9 weeks of age, one week after the administration of the third dose of vaccine. Approximately 38 per cent showed a positive agglutination test in a dilution of 1:3,200; 12 per cent in a dilution of 1:1,600; 7 per cent in a dilution of 1:800, and 13 per cent in a dilution of 1:400. An advancing rise in antibody content with increasing age is apparent in the subsequent tables.

In Table II are listed the agglutinin titers at various age periods in 50 infants in whom the study was carried to completeness. All infants received three doses of vaccine the first injection being given at one week with a booster injection at 6 to 7 months of age.

Thirty-seven of the 50 infants showed a positive agglutination test in a dilution of 1:3,200. Twelve other infants showed a positive agglutination test of 1:400 or better. In one infant the post-booster agglutinin response appeared inadequate.

In general the antibody response was well sustained throughout the period of study. These data would seem to refute the generally held belief that young infants are unable to develop an active immune response following administration of a suitable pertussis vaccine.

In Table III are listed for the purpose of comparison, the agglutinin titers at various age periods in 44 infants in which injections of pertussis vaccine were begun at 2 months of age with a booster dose of vaccine at 6 to 7 months. The immune response as measured by positive agglutination tests are quite comparable with that obtained when pertussis vaccine was administered in the neonatal period.

Thirty-seven of the 44 infants gave a positive agglutination test in a dilution of 1:3,200, one week after the administration of a booster dose of pertussis vaccine. Six other infants showed a post-booster titer of 1:400 or better. In one infant the post-booster agglutinin response appeared inadequate.

Local and systemic reactions to pertussis vaccine were negligible at this early age and were much less frequent and less severe than we were accustomed to observe when pertussis vaccine was administered to infants at the age of 7 months. The fact that a high percentage of parents cooperated to the extent that the study could be completed would seem to justify the impression that local and systemic reactions were inconsequential in nature and frequency.

COMMENT

A satisfactory agglutination response cannot be accepted as an absolute measure of immunity. It can be accepted, however, as a real measure of immune response. The high incidence of positive agglutination tests in high dilutions would seem to justify the expectations that the incidence of pertussis in these vaccinated infants will be less and illness modified should pertussis occur in these inoculated infants. Proof of this assumption will require mass trial over a period of months and years. It is interesting to note that while this study was in progress 2 infants shortly, after the third dose of vaccine,

TABLE III

HOSPITAL NUMBER	4 TO 5 MONTH TITER	6 MONTH TITER	POST-BOOSTER TITER
206199	1:3,200	1:1,600	1:3,200
206349	1:800	1:1,600	1:3,200
206227	1:3,200	1:3,200	1:3,200
205805	1:200	1:50	1:3,200
205633	1:1,600	1:3,200	1:3,200
206095	1:3,200	1:400	1:3,200
206112	–	1:3,200	1:3,200
206744	1:1,600	1:3,200	1:3,200
206763	–	1:1,600	1:3,200
207233	1:3,200	1:3,200	1:3,200
206364	–	1:3,200	1:3,200
C34462	1:3,200	1:3,200	1:3,200
205851	–	1:3,200	1:3,200
345960	–	1:600	1:3,200
208086	1:3,200	1:3,200	1:3,200
207942	–	1:600	1:1,600
208258	1:3,200	1:800	1:3,200
208340	1:400	1:1,600	1:3,200
208324	1:3,200	1:1,600	1:3,200
207623	1:400	1:400	1:1,600
207631	1:800	1:3,200	1:200
207720	1:3,200	1:3,200	1:3,200
207837	1:200	1:800	1:3,200
207721	1:1,600	1:1,600	1:3,200
208865	1:800	1:3,200	1:3,200
208378	1:200	1:400	1:1,600
208681	1:200	1:200	1:3,200
210407	1:1,600	1:1,600	1:1,600
209684	1:3,200	1:3,200	1:3,200
209471	1:400	–	1:3,200
209589	1:400	1:3,200	1:3,200
210004	1:800	1:3,200	1:3,200
209484	1:800	1:1,600	1:800
209485	1:400	1:1,600	1:3,200
210159	1:1,600	1:3,200	1:3,200
C36168	1:1,600	1:3,200	1:3,200
211386	1:3,200	1:3,200	1:3,200
211095	1:3,200	1:3,200	1:800
C36549	1:3,200	1:3,200	1:3,200
211232	1:400	1:3,200	1:3,200
212286	1:800	1:3,200	1:3,200
211864	1:100	1:1,600	1:3,200
212590	1:3,200	1:3,200	1:3,200
212122	1:800	1:3,200	1:3,200

were intimately exposed to pertussis in their homes. They experienced what was thought to be extremely mild pertussis when compared with the illness of other siblings in their respective families. The diagnosis would have been open to serious question had it not been for the history of intimate exposure. It would be difficult to convince the parents of these very young infants that the disease was not materially modified.

During the progress of this study the convincing report of Sako, Treuting, Witt, and Nichamin[3] was published. Their report of more than 16,000 infants below the age of 2 months immunized with alum-precipitated pertussis vaccine and no deaths reported in the state of Louisiana from the immunized group would seem to be indisputable evidence that pertussis can be ameliorated and often prevented by early administration of suitable pertussis vaccine. We agree thoroughly with these workers in their suggestion that the question of

when to immunize against pertussis is urgently in need of clarification. It is our present custom to advise that immunization against pertussis be started at from 6 weeks to 2 months after birth. A booster dose at 7 to 8 months may well be given as an added measure of precaution although this additional dose would not seem necessary in the majority of infants since the antibody content of the blood of vaccinated infants showed little tendency to wane over a period of 6 months, the duration of this study. A satisfactory immune response can be regularly expected when a first dose of pertussis vaccine is administered in the neonatal period. Pertussis vaccine can be safely administered at this early age period without fear of disagreeable local or systemic reactions.

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PARAPERTUSSIS PNEUMONIA

Report of Two Fatal Cases

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THE parapertussis bacillus was first isolated by Eldering and Kendrick[1] from cases of apparently mild whooping cough. The organism is a small nonmotile gram-negative bacillus morphologically resembling *Hemophilus pertussis* but able to grow on non-blood-containing media. It shares minor antigenic factors with *H. pertussis* and *Brucella bronchiseptica*. A general agreement has not been reached as to its exact classification, although it is clear that it is closely related to both of these organisms. All observers agree that infections caused by this organism are considerably milder than the usual picture of pertussis.

We have recently isolated *Bacillus parapertussis** from two fatal cases of "whooping cough" and feel that it is important to point out that infections due to this organism are not always innocuous.

These case reports represent, to our knowledge, the first description of the pathologic findings in human parapertussis infections.

REPORT OF CASES

Case 1.—G. T., a 3-month-old Negro girl, was admitted to Children's Hospital of Michigan on Dec. 20, 1942, with the chief complaint of paroxysmal cough of approximately one week's duration. The illness had begun with symptoms of a cold accompanied from the start by coughing and choking. Considerable phlegm was said to be expectorated. For the last few days the baby had tended to assume a position of opisthotonos frequently associated with "rolling of the eyes." The parents noted fever and had suspected an earache because the baby was noted to pull at both ears.

The past history was noncontributory. Birth and development had been normal. The family history was interesting in that four siblings were all said to have "colds." However, the parents did not feel that any of these children had whooping cough.

Physical examination revealed a well-developed and well-nourished infant in a state of semicoma. The weight was 9 pounds, 14 ounces, the temperature 104.4° F. During the examination the entire body became stiff, the eyes rolled, and opisthotonos was observed. The attack lasted approximately two minutes. The anterior fontanel was widely patent and somewhat depressed. There was an internal strabismus of the left eye. The fundi appeared normal. The tympanic membranes were injected, the nostrils contained small amounts of mucopurulent exudate. There was slight cyanosis of the lips. The pharynx was injected. Examination of the chest revealed moist râles over both bases; the percussion note seemed normal. The liver was felt 4 cm. below the costal margin. The remainder of the findings were noncontributory.

Laboratory data.—Urine was not obtained. The white blood count was 53,000. The differential count revealed 80 per cent lymphocytes and 20 per cent polymorphonuclears. A culture of the blood taken upon admission remained sterile.

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*The term *B. parapertussis* is used for convenience and does not imply classification of the organism in the genus Bacillus.

Course.—The child had repeated paroxysms of coughing during which she became slightly cyanotic but did not vomit. Because of the neurologic symptoms a lumbar puncture was performed shortly after admission. A "bloody tap" was obtained. The supernatant fluid contained an adequate amount of sugar as measured by a rough quantitative test and cultures remained sterile. The patient was placed in an oxygen tent and received subcutaneous injections of 5 per cent sodium sulfadiazine in water. Repeated aspiration of the upper air passages was necessary and a thick mucopurulent material was obtained. During the night the patient had repeated convulsive seizures and severe coughing spells with cyanosis. A definite "whoop" was heard. At times the convulsions were left-sided. The child expired eleven hours after admission to the hospital.

Autopsy.—The examination was performed four hours after death. The body was that of a well-developed and well-nourished infant. External examination revealed no significant abnormalities other than marked abdominal distention and the presence of a small umbilical hernia. The heart was distinctly large owing to dilatation of the right ventricle. The lungs were pink and crepitant except for the hilar central areas which were light purple in color and of medium consistency. A thin mucoid exudate could be expressed from the small bronchi and moderate amounts of tenacious clear mucus were present in the trachea. Aspirated stomach contents filled the lumen of the right main bronchus.

The brain weighed 565 grams (normal 516 grams) and appeared slightly tense against the dura but was not otherwise grossly abnormal. The tympanic cavities contained small amounts of clear fluid.

Microscopic examination: In sections of the lungs there was little involvement of the pulmonary parenchyma proper, but the alveoli here were often found distended to a moderate degree. The significant changes centered around the bronchi of large and medium caliber. The lumina of the structures were usually filled with a mixture of mucus and polymorphonuclear leucocytes. The epithelial lining was more or less densely infiltrated with leucocytes and the cilia often appeared clumped, fused, or entirely absent. There was infiltration with polymorphonuclear leucocytes in the subepithelial layer. The peribronchial connective tissue was wide and infiltrated with predominantly mononuclear cells, lymphocytes, and occasional plasma cells. The capillary plexuses around the bronchi were markedly engorged. The neighboring alveoli occasionally contained a few mononuclear cells but were usually free of exudate. Here and there small groups of alveoli were collapsed.

In the trachea the epithelial lining appeared well preserved and was only mildly infiltrated with polymorphonuclear leucocytes and lymphocytes. Attempts to demonstrate microorganisms in sections of fixed tissue by means of the modified Goodpasture stain were unsuccessful. In paraffin sections of brain tissue stained with hematoxylin-eosin, the only demonstrable change was perivascular edema in many areas and extremely rare pericapillary extravasations in the subcortical white matter.

Bacteriologic studies: A culture of the heart's blood remained sterile. In a smear from the lungs and from the left main bronchus, a few minute gram-negative coccobacilli were found. Pus obtained from a bronchus was cultured on 30 per cent human blood Bordet-Gengou agar. On the fifth day, tiny yellowish colonies without hemolysis appeared, composed of gram-negative pleomorphic bacilli. These organisms grew on subculture at first in two days, and later in one day as tiny colonies on 5 per cent human blood agar and chocolate proteose No. 3 agar. After three transplants they grew freely in tryptose phosphate broth. They were nonmotile, and agglutinated on a slide with anti-*H. pertussis* rabbit serum.* The ability of the organism to grow on nonblood-containing media showed that it was not a virulent strain of *H. pertussis*, nor *Hemophilus influenzae*. However, except for an absence in our cultures of a brownish discoloration of the media, the biochemical properties were those described by Eldering and Kendrick as characteristic of *B. parapertussis*. The strain was identified by Dr. Grace Eldering, Western Division Laboratories, Michigan Department of Health, as the parapertussis bacillus.

**H. pertussis* rabbit antiserum was obtained from Dr. H. C. Batson, Laboratories, Michigan Department of Health, Lansing, Mich.

CASE 2.—E. T., a 13-month-old white girl, was admitted on May 27, 1943, with the chief complaint of "whooping cough."

The child was said to have been well until two weeks before admission when she began to have a dry nonproductive cough which was not accompanied by coryza or fever. There had been whooping cough in the neighborhood and the child was taken to the family physician who made the diagnosis of whooping cough and gave three "injections." During the last week before admission the respirations became rapid, the cough was paroxysmal, and each spasm ended with expectoration of yellowish white mucuslike material. An actual "whoop" was not noted by the parents. For the last few days there was fever and three days before admission a generalized convulsion occurred. Since then the child had eaten almost nothing, the breathing had becoming increasingly rapid, and on the day of admission three other convulsions occurred. After the last convulsion the child became semicomatose and was brought to the hospital.

The past history and family history were noncontributory. The child had developed normally and had not been ill. There had been no immunization against whooping cough or other contagious diseases.

Physical examination revealed an acutely ill, cyanotic, dyspneic child in a state of coma with staring eyes and slight nystagmus. The respirations were extremely rapid and almost entirely abdominal in character. The temperature was 106° F. The lungs were hyper-resonant to percussion everywhere and fine and coarse râles were heard throughout the chest.

Course.—The patient was almost moribund and continued to have convulsions which were mainly right-sided and did not respond to paraldehyde administered by rectum and phenobarbital given intramuscularly. A lumbar puncture was performed yielding a spinal fluid which gave normal values for cells, sugar, and protein. Other laboratory data could not be obtained. The patient expired within eleven hours after admission.

Autopsy.—The examination was performed nine hours after death. Inspection of the body revealed nothing unusual except for slight flaring of the lower portion of the thorax and moderate abdominal distention. There were extensive areas of consolidation, nodular or confluent, in both lungs. The process was especially marked in the apex of the right upper lobe, the apical portion of the right lower lobe, and the left lower lobe which was involved in its entirety, but all lobes were affected. The consolidated areas on cut surface were slightly raised, grayish brown. The bronchi of all calibers contained large amounts of thick yellowish gray mucopurulent exudate, and in the consolidated areas thickening of the bronchial walls was frequently noted.

The brain weighed 804 grams (normal 925 grams) and did not appear grossly abnormal. Considerable amounts of thick purulent yellow exudate were present in both tympanic cavities.

Microscopic examination: The process in the lungs was essentially similar to that described in Case 1, but much more severe and extensive and complicated by the presence of a widespread exudate of polymorphonuclear leucocytes and mononuclear cells in the alveolar lumina. The bronchial epithelium was often destroyed by ulceration and necrosis. In sections stained with modified Goodpasture stain, small slightly pleomorphic gram-negative bacteria were often demonstrable within the cytoplasm of polymorphonuclear leucocytes and mononuclear cells, but were not found within the epithelium of the bronchi. Except for congestion and evidence of cerebral edema, sections of the brain were not remarkable.

Bacteriologic studies: Pus from the bronchus was planted on 30 per cent human blood Bordet-Gengou medium. After six days' incubation a variety of gram-negative and gram-positive cocci had grown but there were no pertussis-like colonies. Material from the lung was inoculated on 5 per cent human blood chocolate proteose No. 3 agar. After twenty-four hours' incubation there were a few small grayish colonies composed of short poorly staining gram-negative bacilli. These organisms agglutinated on a slide with anti-*H. pertussis* rabbit serum. Pus from the right tympanic cavity grew *Micrococcus catarrhalis* and *Streptococcus hemolyticus.* The left tympanic cavity produced a growth on blood agar

in two days of tiny rounded colonies without hemolysis, composed of thin regular gram-negative bacilli. These organisms grew well on chocolate agar subcultures and also gave a positive slide agglutination with anti-*H. pertussis* serum. The strain from the ear was submitted to Dr. Eldering for confirmation and she reported: "The culture is a gram-negative coccobacillus, produces hemolysis in Bordet-Gengou medium, grows well on veal infusion agar with formation of brown pigment. The organisms were agglutinated by serum prepared against Hemophilus pertussis at a titer of 1:20, Br. bronchiseptica at a titer of 1:100, and parapertussis bacilli at a titer of 1:2,000."

DISCUSSION

Bradford and Slavin,[2] and Miller, Saito, and Silverberg[3] also isolated *B. parapertussis* from children with severe cough and extended Eldering and Kendrick's[1] observations. Miller and his co-workers, and Flosdorf, Biondi, Felton, and McGuinness[4] observed that specific humoral antibodies were present in the blood serum of 25 to 70 per cent of normal children.

By means of absorption experiments, Flosdorf and his co-workers were able to conclude that these agglutinins represented previous specific infections with the parapertussis bacillus and not nonspecific cross-reactions due to previous infections with, or immunization against *H. pertussis*. This evidence "suggests that only the relatively serious cases of parapertussis are diagnosed clinically and that these are similar to mild cases of whooping cough; the nature of the typical disease of parapertussis apparently is not recognized clinically in relation to the specific etiologic agent."[4]

While no second attacks of parapertussis have been reported, the disease has been noted in children who have had pertussis and in children who have been immunized with pertussis vaccine; conversely, pertussis has been observed in children who have had parapertussis.

In Case 1 no definite history of exposure to recognized whooping cough was obtained, but upper respiratory infection associated with cough existed simultaneously in the patient's four siblings. In Case 2 the exposure to "whooping cough" was definite. The clinical picture and the pathologic findings in both cases were compatible with pertussis. The high lymphocyte count in Case 1 and the encephalopathy in both cases seemed to corroborate this diagnosis.

In view of the implications which our two cases carry in regard to the exact etiologic diagnosis of pertussis-like infections, it is essential to establish an accurate diagnosis in each of them. The diagnostic criteria for the bacteriologic identification of the parapertussis bacillus have been fulfilled in both instances.

Since the pathologic processes described are in most respects similar to those encountered in pertussis pneumonia, and since Miller isolated one of his strains of *B. parapertussis* along with phase I *H. pertussis* from a severe case of whooping cough,[5] one should be able to prove the absence of *H. pertussis* in order to attribute the etiology to *B. parapertussis*. The only material cultured expressly for *H. pertussis* was the bronchial secretion. These cultures, however, were examined carefully for *H. pertussis* which was not found. It would be

more convincing if the material from the lungs had been so cultured. In Case 1 the lung culture was sterile. In Case 2 the parapertussis bacillus was isolated from the lung in pure culture, and from the ear, an unlikely occurrence if the organisms were merely secondary invaders. Therefore, it is reasonable to conclude that *B. parapertussis* was responsible for the fatal disease in each case.

The frequency with which parapertussis can cause serious and even fatal forms of "whooping cough" remains to be determined. Judging from our experience until 1942, few attempts are made in routine pathologic work to establish on an accurate bacteriologic basis the etiology of cases of whooping cough at autopsy. The pathologist is usually satisfied to render a diagnosis of interstitial pneumonia compatible with whooping cough, and means for the exact identification of pertussis-like organisms are not always available. It is quite possible that the two cases reported were rare exceptions to the rule that parapertussis infections are not fatal, but the occurrence of these two cases within less than one year would suggest the opposite. Only painstaking observations made jointly by the clinician, pathologist, and bacteriologist can settle this point. Since parapertussis bacillus is not included in the whooping cough vaccines now recommended, and since there appears to be little cross-immunity between infections with *H. pertussis* and *B. parapertussis*, the problem is obviously of more than theoretic importance.

SUMMARY

1. Two cases of fatal pertussis-like infections in infants are reported with autopsy studies.

2. The etiologic agent was demonstrated to be *B. parapertussis*, instead of *H. pertussis*, upon bacteriologic, rather than pathologic, evidence.

3. The diagnosis of pertussis at autopsy should not be made without bacteriologic confirmation.

4. Parapertussis may be a more serious disease than formerly thought.

The authors wish to express their indebtedness to Dr. Grace Eldering and Dr. Pearl Kendrick for confirming the organisms isolated, and for their helpful suggestions.

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MISTREATMENT OF CONGENITAL HEMOLYTIC DISEASE (ERYTHROBLASTOSIS FETALIS) BY TRANSFUSIONS OF Rh-POSITIVE BLOOD AND MATERNAL SERUM

A Case Report

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SO MUCH evidence[1-8] has now accumulated demonstrating the superiority of Rh-negative blood over Rh-positive blood in the treatment of congenital hemolytic disease caused by Rh sensitization, that it seems hardly necessary to reiterate this point. However, a recent letter to the editor of the *Journal of the American Medical Association*[9] and an article recently published in the JOURNAL OF PEDIATRICS[10] show that misconceptions concerning the pathogenesis and treatment of this disease still exist. The latter article appeared even though the fallacies in the former had been pointed out by Diamond and Denton[11] and by Liber.[12] It seems to us that only misinformed or misguided physicians would nowadays treat such cases with Rh-positive blood; unfortunately, such physicians would not be qualified to evaluate critically the results of their treatment. An exception to this statement is the report by Brandes and Cushman.[13] These authors described an infant with severe hemolytic disease who failed to improve despite transfusions of a total of 220 c.c. of Rh-positive blood (an amount almost equal to the total blood volume), but who then rapidly and completely recovered after two transfusions of a total of only 160 c.c. of Rh-negative blood. In the carefully controlled study by Mollison,[14] in which erythroblastotic infants were transfused with mixtures of Rh-positive and Rh-negative blood, the Rh-negative blood survived in the infant circulations for periods of two to three months while the Rh-positive blood was eliminated within a period of several hours or days.

Since, in the present state of our knowledge of this subject, we do not feel that deliberate transfusions of Rh-positive blood to erythroblastotic infants are justifiable, we were morally prevented from performing further experiments along these lines. It occurred to us that a search of hospital records should reveal suitable examples of mistreated cases of congenital hemolytic disease in the days before the Rh factor was known. Our expectations have been fully satisfied and several such cases were found without difficulty. The purpose of this paper is to describe one of these cases, which may help convince even the most obstinate skeptic.

From the Blood Transfusion Division, Department of Laboratories, the Jewish Hospital of Brooklyn.
Read before the Society for the Study of the Blood, May 15, 1946.

CASE REPORT

L. H., the mother of our patient, gave the following obstetric history: The first pregnancy ended at term, Oct. 1, 1935, with the delivery of a normal female infant weighing 8 pounds, 3 ounces. This girl never showed any signs of anemia or jaundice during the neonatal period and at 10½ years of age was in good health.

The second pregnancy also ended at term, in September, 1939, when a female child was born. This infant, our patient, developed jaundice and anemia shortly after birth, and died at the age of 5 weeks as a result of improper transfusion therapy.

The third pregnancy terminated on July 15, 1942, with an 8-month stillborn female fetus which had been dead in utero for three weeks before delivery.

The results of grouping and Rh tests of the mother, father, and the living sibling are shown in Table I.

TABLE I

BLOOD OF	GROUP	MN TYPE*	Rh-Hr TYPE
Patient's father	O	MN	Rh_1Rh_1
Patient's mother	O	N	rh
Patient's sister	O	N	Rh_1rh

*The MN type is hardly ever of clinical importance and is included only for the sake of completeness.

It will be seen that in accordance with the expectations from the obstetric history, the patient's mother is Rh negative while the father is almost surely homozygous for the Rh factor because he belongs to subtype Rh_1Rh_1, i.e., he is Hr negative.* Presumably, the mother became sensitized as a result of her first pregnancy because it will be seen that the living child, although herself unaffected, is Rh positive (subtype Rh_1rh). Since the second child, our patient, also had to be Rh positive for genetic reasons, she developed congenital hemolytic disease. Moreover, at the time of delivery, some of this infant's blood gained access to her mother's circulation and increased the degree of the mother's sensitization. This accounts for the stillbirth at the third delivery. This history is typical of so-called univalent antibody disease, in accordance with Wiener's theory.[16] Univalent antibodies (glutinins or blockers), being comprised of smaller molecules than bivalent or multivalent antibodies (agglutinins), can traverse the placenta into the fetal circulation during pregnancy, thus giving rise to anemia or, in more severe cases, to stillbirths with hydrops.[17]

Our tests for Rh sensitization were performed in April, 1946, almost four years after the last delivery, so that ample time had elapsed for the antibody titer to fall. In tests carried out by the agglutination technique, Rh antibodies of only one unit titer were demonstrable, while by the conglutination technique,[18] the antibody titer was two units. The fact that the titer was higher in plasma media than in saline is evidence that the patient's serum contained univalent as well as bivalent antibodies, in accordance with the requirements of the theory.

The clinical history of the patient in whom we are primarily interested is: The infant was born on Sept. 2, 1939, at 11:20 A.M. after a six-hour labor, terminating with a spontaneous delivery. Her condition at birth was good, the weight being 7 pounds, 8 ounces, and the length 49 cm. The vernix was yellow. There was faint cyanosis about the mouth and slight dyspnea, but the infant was normally active. The liver was enlarged to three finger-breadths below the costal margin but the spleen was not palpable at first.

The following morning, the baby's skin was noted to be slightly icteric. A blood count showed 70 per cent hemoglobin concentration with 3,600,000 red cells per cubic millimeter, and the blood smear showed 50 nucleated red cells for each 100 white cells. The infant was treated with repeated blood transfusions, the father and the father's brother† acting as donors for almost all of them. The first transfusion was given in the afternoon of September 3, 80 c.c. of the father's blood being injected. The following day the hemo-

*For the latest improved nomenclature of the Rh-Hr types, see Wiener and associates.[15]
†Recent tests showed this individual to belong to type ON Rh_1rh.

globin was 93 per cent but, by September 5, the hemoglobin concentration had dropped back to 77 per cent, the jaundice was more pronounced, and the infant was somewhat more listless. Despite this, the number of nucleated red cells had dropped to one per 100 white cells. Thereafter the blood smears were practically free of nucleated red cells.

The patient was given two small subcutaneous injections of whole citrated blood and serum from the family donors as well as intravenous injections of 75 to 85 c.c. of citrated blood. Despite this, the hemoglobin concentration ranged between 60 and 75 per cent. The jaundice became deeper, the liver and spleen remained enlarged, and the abdomen was distended. In addition, the infant was listless, nursed poorly, and slept most of the time.

After the mother was discharged from the hospital on the ninth day, the infant was transferred to the pediatric service where the same treatment was continued; namely, transfusions of whole citrated blood from the father and uncle.

TABLE II

DATE	HEMOGLOBIN (PER CENT)	ERYTHROCYTES (MILLIONS PER CU. MM.)	NUCLEATED R.B.C. PER 100 W.B.C.	INTRAVENOUS BLOOD TRANSFUSIONS	OTHER INJECTIONS
Sept. 2, 1939			50		
3	70	3.60	36	80 c.c.	
4	93	---	22		
5	77	3.80	1		40 c.c. blood subcutaneously
6	94	4.80		40 c.c.	
7	74	3.60			40 c.c. blood subcutaneously
8	67	2.26			20 c.c. serum (uncle's, subcutaneously)
9	60	2.25		75 c.c.	
10	66	1.83		85 c.c.	
11	75	3.27			
12	74	2.94	1		
13	71	3.01			
14	74	3.08			
15	74	3.50			
16	71	2.97			
18	67	2.31		75 c.c.	
19	--	---		90 c.c.	
20	81	3.98			
23	74	3.76			
26	67	3.12			
27	--	---		50 c.c.	
28	--	---		45 c.c.	
29	74	3.48	Reticulocytes 40/1,000		
Oct. 1, 1939	74	3.61			
3	56	2.14			
4	50				0.5 c.c. liver extract
5	--	---			20.0 c.c. maternal serum
6	28	1.28	Reticulocytes 60/1,000	75 c.c.	5.0 c.c. maternal serum
7	Exitus			Total: 615 c.c. blood	

A summary of the blood counts and transfusions is given in Table II. It will be seen that while the usual case of congenital hemolytic disease nowadays rarely requires more than 250 c.c. of blood to effectuate a permanent cure when Rh-negative donors are used, this child, by October 5, at the age of 33 days, had received a total of 615 c.c. of blood intravenously without noticeable improvement. The jaundice was still present; the liver and spleen were hard, the former four fingerbreadths and the latter two fingerbreadths

below the costal margin. Despite parenteral liver and iron therapy as well as blood transfusions, the blood count continued to drop until, on October 5, it was only 50 per cent.

At this time a report was found in the medical literature claiming favorable results from intramuscular injections of maternal serum in cases of erythroblastosis fetalis. Consequently, 20 c.c. of maternal serum were injected into the infant, and the subsequent course demonstrated the harmful results of such premature publications of new therapeutic procedures.

The following morning the blood count was found to have dropped precipitously, the hemoglobin concentration being only 28 per cent and the red cell count 1,280,000. The infant, who for a while had been quite active and playful, became listless once more, and did not take her feedings well. The connection between this reaction and the serum injection not being appreciated at the time, another 5 c.c. of maternal serum were injected. Because of the infant's desperate condition, 75 c.c. of citrated blood from a new donor were also transfused. Twenty minutes after the transfusion was completed, the infant's respirations became grunting and rapid, and her extremities cold and cyanotic. She was treated for peripheral collapse. During the night she voided a small quantity (5 c.c.) of dark amber urine which gave a positive reaction for bile and blood although no red cells were seen microscopically. The temperature rose to 103.6° F. The following morning at 7:30 A.M., the infant suddenly vomited about 3 ounces of black material which gave a 4 plus benzidine reaction. The respirations became gasping and the infant died ten minutes later.

The following were the pertinent post-mortem findings as reported by Dr. David M. Grayzel: gross examination revealed marked yellow-green discoloration of the skin and conjunctivae. There was no edema of the skin, and no free fluid in any of the body cavities. In the chest subpleural and subpericardial petechiae were noted. The stomach contained yellow-green and dark brown material, and its mucous membrane was discolored yellow-green. All the organs showed yellow-green discoloration on section. There was marked hepatomegaly (liver weighed 342 grams; average normal for age only 120 grams) and splenomegaly (spleen weighed 60 grams; average normal only 16 grams). The kidneys were normal in size, and the cortex and medulla were well demarcated. There was marked hyperplasia of the bone marrow. The brain showed no kernicterus. Microscopic examination of the liver showed inspissated casts of bile pigment in the canaliculi, and numerous islands of hematopoiesis. No agglutination thrombi were found in the brain. The kidneys showed numerous hemoglobin casts and occasional red cell casts in the collecting tubules.

There is no doubt that the patient's prolonged illness and eventual death were due to the improper treatment, which in turn was caused by lack of understanding of the pathogenesis of the disease at the time when this infant was born. The use of Rh-positive blood was ineffectual because the patient's body contained an excess of univalent Rh antibody, sufficient not only to destroy all of her own blood but also the additional Rh-positive blood introduced by transfusion. One of us (A. S. W.) has shown[17, 18] that such patients respond rapidly to transfusions of Rh-negative blood even though the presence of univalent Rh antibodies can be demonstrated in their serum for periods of a month or longer. These antibodies apparently do no harm as long as no "fuel is added to the fire," and they are gradually eliminated from the body. As long as they are present, they do destroy any new Rh-positive red cells produced by the infant as soon as they enter the circulation. This process is so gradual, however, that the body readily eliminates the products of this blood destruction without harm. The final disappearance of the antibodies and resulting cure is heralded by the appearance of reticulocytes in the blood smear, which usually occurs about the sixth week. Naturally, when the in-

fant's body contains only small amounts of Rh antibodies, the disease is self-limited and recovery follows quickly whether Rh-positive or Rh-negative blood is transfused.

The culminating insult in this case, of course, was the injection of maternal serum, particularly at a time when the maternal antibody titer was near its peak.* This brought about a pronounced exacerbation of the hemolysis and the infant's death, just at a time when recovery was to be expected.

COMMENT

The argument for the use of Rh-positive blood when treating erythroblastotic infants, in order to absorb the excess antibodies and thus bring about a cure more rapidly, is fallacious. The body can adapt itself to many things provided sufficient time is allowed. For example, an acute hemorrhage of only one-third of the total blood volume may cause death, while slow bleeding, depleting as much as 80 per cent of the red cells, is not incompatible with life.

The other argument that Rh-negative blood donors are not always available is also untrue, because the mother, who is the ideal donor for all cases of erythroblastosis, including those due to A-B sensitization,† is usually at hand. The only precaution required is that the mother's red cells be washed with saline solution in order to remove the plasma containing the harmful antibody. Since infants require relatively small quantities of blood, the procedure of washing the red cells can be carried out in culture tubes in an ordinary laboratory centrifuge. Two washings are sufficient and since all grouping and matching tests may be omitted when maternal red cells are transfused,[6] this takes even less time than the regular procedure, especially when, as is sometimes necessary, one must wait for long periods for professional donors to make their appearance.

Incidentally, we prefer to use fresh blood rather than bank blood for treating erythroblastotic infants, as overage blood will break down faster in the circulation. Thus, fresh blood is more efficient than stored blood of uncertain age or of an uncertain state of preservation. The use of maternal blood is also more convenient because, following the second washing, it is possible to remove the entire supernatant fluid leaving the packed cells which can then be transfused by adding only a minimal amount of saline to reduce the viscosity. In this way a double dose of red cells can be given in the same small volume at a single transfusion, and rarely are more than two or three such transfusions required to effectuate a permanent cure.

SUMMARY

A case is presented which demonstrates the ineffectiveness of Rh-positive blood as compared with Rh-negative blood, and the danger of the use of maternal serum when treating infants with congenital hemolytic disease.

*"The antibody titer usually rises during the fortnight following the delivery."[3]

†In cases due to A-B sensitization, it is our practice to add 10 c.c. of Witebsky's solution of group substances to the washed maternal red cells; we also inject 10 c.c. of the group substance into the umbilical cord vein at birth.

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ADDENDUM

While this article was in press, a report by Sanford and Gerstley[20] appeared, which illustrates again the importance of using washed maternal cells for transfusing erythroblastotic infants, in cases where the exact pathogenesis is obscure. The patient had to be given the tremendous total of 2,200 c.c. of blood before the hemolytic process was arrested, whereas one-tenth of that amount of blood usually suffices when washed maternal cells are used. The grouping results (mother subgroup A,B) suggest that the abnormal antibody in the maternal serum must have been an anti-O agglutinin, as in the case recently reported by Henry.[21] If this conclusion is correct, then transfusions of blood of subgroup A,B would have been equally satisfactory, in case there was any objection to the use of maternal blood.

ERYTHROBLASTIC ANEMIA OF COOLEY

Observations on the Effect of Splenectomy Performed on Identical Twins

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COOLEY and Lee[1] in 1925, clearly defined a clinical syndrome which they later designated as "erythroblastic anemia."[2] In so doing they differentiated erythroblastic anemia from a large group of unrelated anemias and splenomegalies that occur in children.

The distinctive features of the disease in its classical form are so well known that they merit only brief mention. The condition, usually attributed to a developmental defect of the hemopoietic system, is characterized by a severe and progressing anemia with large numbers of erythroblasts in the peripheral blood; a constant racial and familial incidence; enlargement of the spleen and liver; x-ray and histologic changes in the bones; pigment abnormalities; and mongoloid facies.

Despite innumerable investigations in which various substances and procedures have been tried in an attempt to find a remedy for this condition, none has proved successful. The majority of therapeutic measures tried produced no effect; transfusions temporarily alleviate the symptoms; certain other measures have been too incompletely studied to permit any definite conclusions regarding their effectiveness. Into this latter group is the operative removal of the spleen. The reports concerning the effect of splenectomy are contradictory. A few writers, Baty, Blackfan, and Diamond[3] and Custer[4] describe the operation as failing to modify the symptoms, while others, Hitzrot,[5] Cooley and Lee,[6] and Whipple and his co-workers,[7] describe the beneficial effects.

In view of this inconclusive evidence, this report recording the striking good effects of splenectomy in identical twins seems justified. The twins were suffering from a classical form of the disease, which in each child appeared to be of equal severity. Soon after admission the spleen was removed from one child. Both twins were then followed for fifteen months. The effects of the splenectomy were so spectacularly successful that fifteen months later a splenectomy was performed on the other. The results of the observations are described:

The identical twins, N. and A. P., were male children of Greek parentage, born in this country May 10, 1938. The birth weights were 5 pounds and 5 pounds, 1 ounce, respectively. Both were considered well until the age of 10 months, at which time a severe anemia was first recognized. Both were studied and treated in the hematological clinic at the New York Hospital, and at the time of admission to the Harriet Lane Home (Oct. 10, 1943) presented the following picture:

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N. P. (A-32420), aged 5 years, 5 months, was pale but active. He had a typical monogoloid facies. The skin and sclerae were a muddy yellow color. The eyes were slanting. The heart was enlarged and a loud blowing systolic murmur was heard over the precordium. The murmur was thought to be hemic in origin. The abdomen was protuberant and the liver edge was palpable two fingerbreadths below the costal margin. The edge of the spleen extended to the crest of the ilium and filled the whole left side of the abdomen. X-ray examination of the bones revealed the characteristic changes of Cooley's anemia.

A. P. (A-32419) was pale and not very active. He likewise had a typical mongoloid facies with muddy yellow skin and slanting eyes. Both the skin and sclerae were moderately icteric. The heart, like that of his brother, was slightly enlarged and a loud hemic murmur, systolic in time, was heard over the precordium. The striated muscle tone was poor and the abdomen was protuberant. The liver extended two fingerbreadths below the costal margin and the tip of the spleen to and into the iliac fossa. X-ray examination revealed changes in the skeleton similar to those of the brother and were characteristic of Cooley's anemia.

	N. P.	A. P.
STS	Neg.	Neg.
RBC	1,690,000	1,760,000
Hbg (Sahli)	4 grams	4 grams
WBC	12,500	14,800
Nucleated RBC per 100 WBC	10	10
Reticulocytes (per cent)	4	4
Platelets	145,000	205,000
Van den Bergh	1.6	I.I.–13
Fragility Test		
Hemolysis began	0.66	0.66 (control 0.42)
Incomplete at	0.21	0.21 (control incomplete at 0.21)

Soon after the twins were hospitalized, blood studies were performed on the parents, who were Greek émigrés. That of the father was found to be normal, but the mother's blood showed a marked anisocytosis and poikilocytosis. Although it did not contain erythroblasts and little evidence of anemia was found, the mother was considered to exhibit a trait of Cooley's anemia and possibly to harbor a defective gene capable of producing the disease in her offspring.

On admission to the hospital, except for a height difference of 1 to 2 cm. and a weight difference of 0.6 kg. in favor of A. P., the twins presented almost identical x-ray, clinical, and laboratory findings. Initial treatment consisted of bed rest and repeated transfusions of whole blood. This form of therapy was continued over a five-month period during which time the clinical picture and blood studies showed little change. In March, 1943, five months after admission, the spleen was removed from A. P. Until time of operation both boys had gained 0.5 kg. and had required essentially the same amount of blood by transfusion to maintain a hemoglobin content above 5 Gm. per 100 c.c. of blood.

EFFECTS OF SPLENECTOMY

During the 15 months following the operation on A. P., he grew taller and gained more weight than his twin. Further, the splenectomized twin needed only one-third to one-fifth the amount of blood required by his unoperated brother.

In May, 1945, fourteen months after the splenectomy on A. P., it became apparent that N. P. was gradually requiring larger and larger amounts of blood to maintain a level of 5 Gm. hemoglobin per 100 c.c. of blood. Although no quantitative determination of the urobilin excretion in the urine and feces was made at this time, determinations of urinary iron excretion and Van den

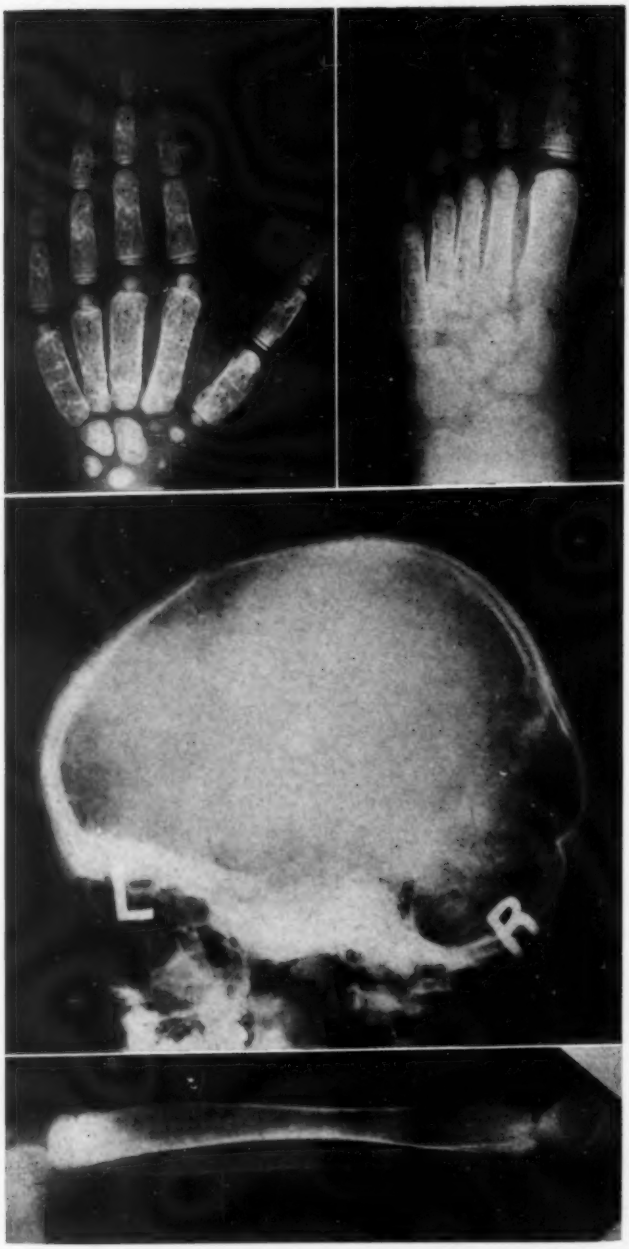


Fig. 1.—Photograph of x-ray films of long bones, hands, feet, and skull of N. P.

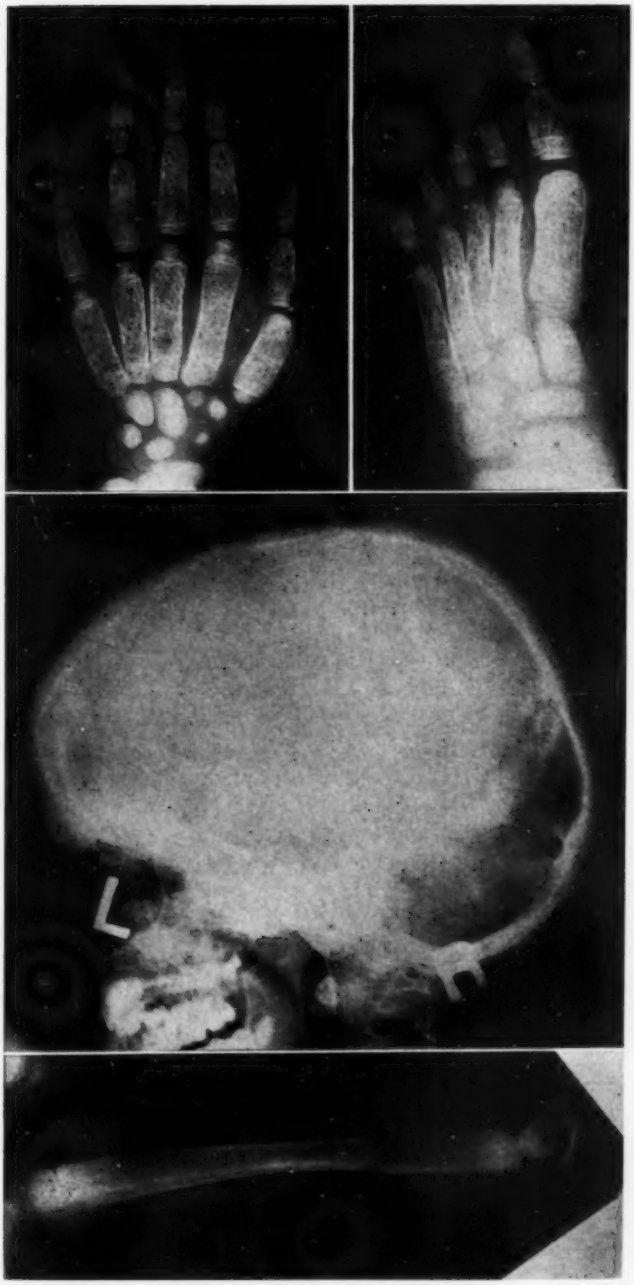


Fig. 2.—Photograph of x-ray films of long bones, hands, feet, and skull of A. P.

Bergh tests showed no evidence of hemolysis. For these reasons and because N. P.'s spleen was so enormous, it was removed.

The effect of splenectomy in the two children is shown in Charts I, II, III, and IV. The changes that occurred in both were clear-cut and essentially the same. Neither child was cured, but in each the symptoms were greatly alleviated. The most striking result following the removal of the spleen was

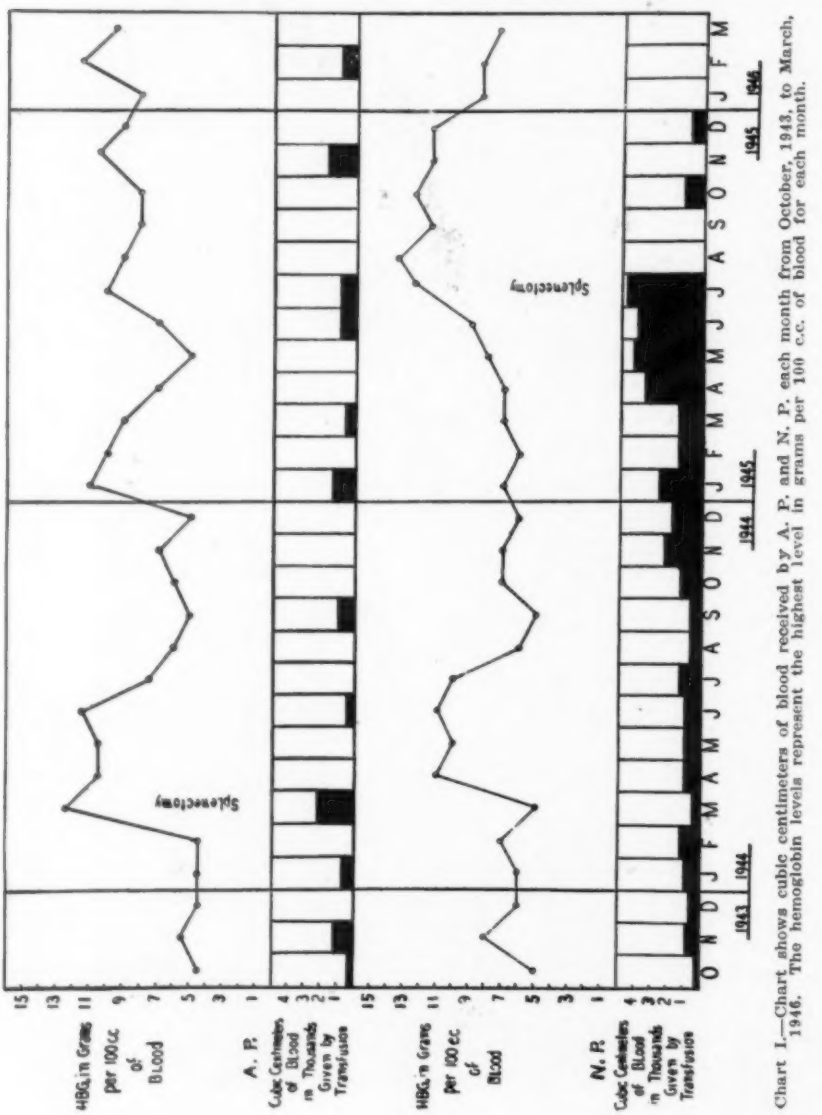

HBG. in Grams per 100 cc of Blood
A. P.
Cubic Centimeters of Blood in Thousands Given by Transfusion
Splenectomy
HBG. in Grams per 100 cc of Blood
N. P.
Cubic Centimeters of Blood in Thousands Given by Transfusion
Splenectomy
O N D J F M A M J J A S O N D J F M
1943 1944 1945 1946

Chart I.—Chart shows cubic centimeters of blood received by A. P. and N. P. each month from October, 1943, to March, 1946. The hemoglobin levels represent the highest level in grams per 100 c.c. of blood for each month.

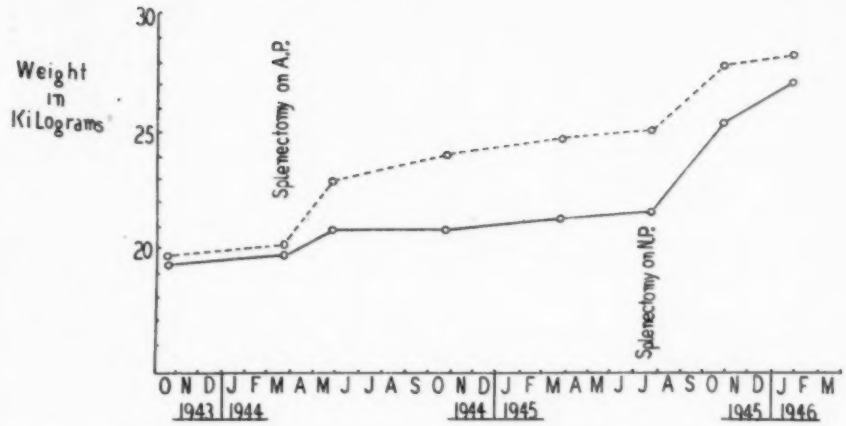
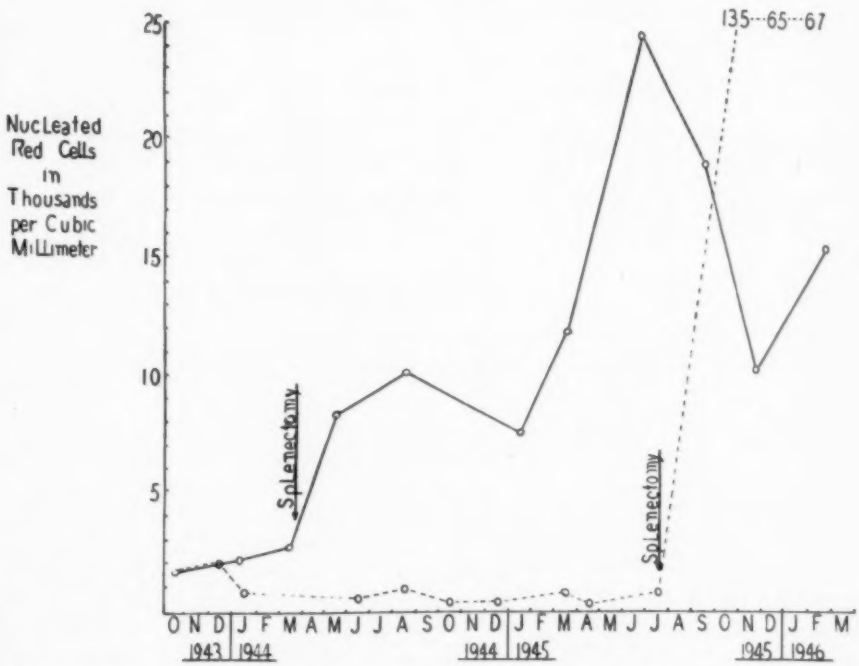

Weight
in
Kilograms
30
25
20
Splenectomy on A.P.
Splenectomy on N.P.
O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M
1943 1944 1944 1945 1945 1946

Chart II.—Chart shows weight in kilograms of the twins from October, 1943, to January, 1946. Broken line, A. P.; solid line, N. P.



Charl III.—Chart shows the effect of splenectomy on the number of nucleated red cells per cubic millimeter. Solid line, A. P.; broken line, N. P.

that transfusions needed to maintain a critical level of 5 Gm. hemoglobin per 100 c.c. were required at two- to four-month intervals in contrast to the transfusions required weekly before operation. Also each twin made substantial weight gains following the operation and in February, 1946, N. P. had improved to such an extent that he had become comparable to his brother in signs and symptoms.

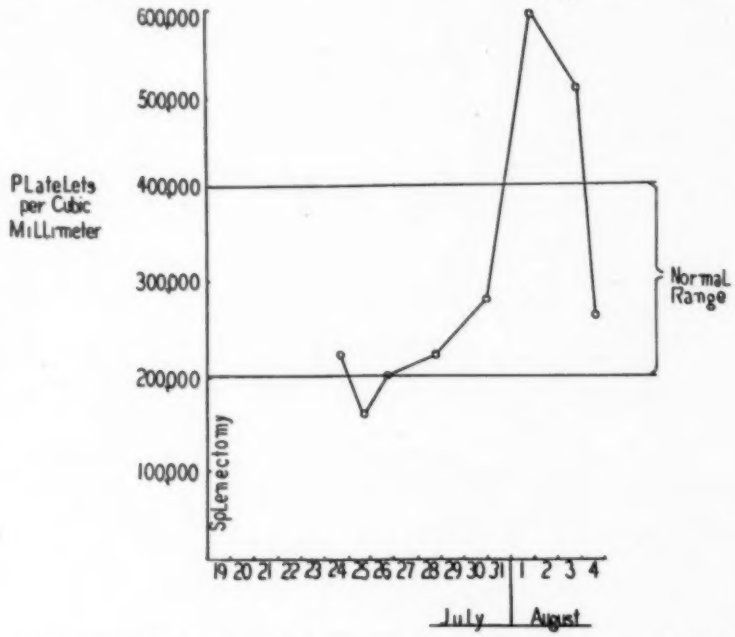


Chart IV.—Chart shows effect of splenectomy in N. P. upon the number of platelets.

EFECT OF SPLENECTOMY ON THE BLOOD

The remarkable changes which occur in the peripheral blood following the removal of the spleen have been adequately described by numerous observers, Baty, Blackfan, and Diamond,[3] Whipple, Reeves, and Cobb,[7] Bradford and Dye,[8] and Cooley, Witwer, and Lee.[2] Similar changes were observed in the twins here reported. The red cell count and hemoglobin content remained essentially unchanged. There was an increase in the number of leucocytes, immature cells, and platelets. Except for the striking and persistent change in the number of nucleated red cells, the changes that occurred following splenectomy in these patients with Cooley's anemia appear to be not unlike those that occur following splenectomy in the normal individual. The nucleated red cells, however, increased in number immediately after the spleen was removed in both children and have persisted since operation. In February, 1946, 10,000 to 15,000 nucleated red cells per cubic millimeter were found in the blood of A. P. and 60,000 nucleated red cells were found in the blood of N. P.

The changes in the number of blood platelets followed a pattern described by Connors.[9] The platelets began to increase seven days after splenectomy and reached a maximum thirteen days after operation and then gradually returned to normal (Chart IV).

DISCUSSION

The effect of splenectomy in these two children has been striking and beneficial. Whether the improvement is only temporary remains to be determined. The changes, however, have persisted for two years in A. P. and a similar effect has been observed in N. P. for nine months, to the time of this report (March, 1946). Besides causing the improvements noted, removal of the large splenic mass increased the comfort of the children.

The explanation of why splenectomy modified the symptoms in these children is not clear. We know that to maintain a given blood level, the rate of blood destruction must equal the rate of blood formation. In patients with Cooley's anemia one or both of these functions fails and to sustain life repeated infusions of blood are necessary. The manner in which the spleen affects either of these functions is obscure, but it was obvious that following splenectomy much less transfused blood became necessary to maintain a level of 5 Gm. (critical level) hemoglobin per 100 c.c. of blood. The large amounts of blood necessary to maintain this level in N. P. before operation suggest increased blood destruction, although the destruction was not reflected by an increased iron excretion in the urine or an elevation of the Van den Bergh. The former was performed on four successive occasions. Further, the deposits of iron pigment in the liver and spleen were not sufficient to account for all of the iron which was being liberated by the destroyed cells. The inference seemed to be that the breakdown products of the red cells were being promptly utilized within the body for new blood formation.

SUMMARY

The observations on the striking good effect of splenectomy on identical twins suffering from erythroblastic anemia of Cooley are recorded.

The twins following splenectomy required only one-third to one-fifth the amount of blood to maintain a level of 5 Gm. hemoglobin (critical level) per 100 c.c. of blood than before operation. Both children made substantial weight gains and were greatly improved symptomatically following the operation.

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ERYTHEMA MULTIFORME

With Special Emphasis on Postvaccinal Erythema

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THE etiology of erythema multiforme remains unknown, although many theories as to its origin have been advocated, such as toxic, bacterial, virus, or allergic factors. At times this syndrome seems to appear spontaneously without any associated illness. However, various observers have noted that this symptom complex may be associated in some instances with herpes simplex,[1] sulfonamide sensitivity,[2] Vincent's infections, rheumatic fever, and occasionally with smallpox vaccination.[2-6]

During the period from July to December, 1945, we have had the opportunity of observing three cases of erythema multiforme with involvement of the skin and mucous membrane following smallpox vaccination. Coincident involvement of skin, oral mucosa, and the conjunctivae has been termed the Stevens-Johnson syndrome. Murphy[7] has suggested that this syndrome should be separated from erythema multiforme in which no changes of the mucous membrane are found, but this appears to be a matter of definition, as the pathogenesis is probably the same. Also, we are reporting three other cases of erythema multiforme of seemingly diverse etiology. One such case was associated with acute rheumatic fever, one followed the administration of horse serum, and one case had no discernible etiologic factor.

Postvaccinal Rashes. Review of the Literature.—Smallpox vaccinations are occasionally followed by skin eruptions of various types. Bloch[6] classifies these eruptions as: (1) papular; (2) urticarial and erythematous, including papular urticaria, erythema multiforme, morbilliform erythema, scarlatiniform erythema, roseola, urticaria, erythema iris, nummular erythema, erythema, and red urticaria; (3) purpuric petechial; (4) pustular, including bullous impetigo, folliculitis, pustular erythema, exfoliative dermatitis; (5) eczematoid. Heaton[8] reports a purpuric rash following vaccination, as do Davidson and Davis.[9] Chalke[10] describes rashes of papular type, morbilliform and maculopapular lesions subsequent to vaccination. The cause of some of these rashes is occasionally obvious, such as the spread of vaccinia virus to the surrounding skin by scratching, or generalized spread as may occur in the presence of eczema. On the other hand, the cause of lesions of the skin and mucous membrane such as appear in erythema multiforme is not known. Eichenlaub[3] suggests that the etiologic factor may be a foreign protein in the vaccine or in the cowpox virus itself, or some antitoxin produced by the body. Chalke[5] attempts to explain this type of rash as due to absorption either of toxic products from the vaccinal pustule, or of the lymph of the vaccine. Ricketts and Byles, to

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quote Bloch,[6] attribute the erythematous lesions to circulation in the blood stream of secondary products of inflammation absorbed from the pustule, and regard the particulate eruptions as toxemic and not implying generalized spread of the specific virus. Davidson and Davis offer an allergic tendency as a possible explanation for these vaccinal reactions.

Incidence.—The incidence of erythema multiforme following vaccination must be exceedingly small. Almost every patient who enters the San Francisco Hospital is routinely vaccinated (approximately 14,600 admissions a year), and yet we can find no record of the occurrence of erythema multiforme in any patients except those reported here. Sobel[11] found 80 cases of generalized eruptions in 4,160 vaccinations. Eichenlaub[3] reported only one case of generalized dermatosis in 10,000 vaccinations. Director[4] described one case of postvaccinal exanthem among 122,000 vaccinations. Among one-half million vaccinations, Bloch[6] found 123 regional or general eruptions. Of the 123, twenty were erythema multiforme, and four were erythema iris. Chalke reported 14 children with eruptions among 1,600 vaccinated.

Erythema multiforme may follow primary or revaccinations. Of our three patients, two suffered from the disease following an initial vaccination, and one following revaccination. This last was a vaccinoid reaction.

CASE REPORTS

CASE 1.—R. O., aged 17 months, white, male, entered the San Francisco Hospital with the complaint of a rash of two days' duration. He had been successfully vaccinated ten days prior to entry. Two days before entry some "red marks" were noted on the left shoulder, upper left arm, and behind the left ear. Soon afterward larger red blotches appeared over the upper trunk and neck. The eruption behind the ear bled, but the others did not. The child became feverish and irritable and refused everything by mouth. The family physician noted lesions in the mouth the day before hospitalization but no treatment was given. Past history disclosed only an attack of chickenpox several months previously.

Examination revealed the rectal temperature to be 99° F. The child was very irritable. Pleomorphic skin lesions varying from pustules to discrete and confluent irregular maculopapules were noted on the face, especially the forehead, the neck, shoulders, back, and upper left arm. The cervical and axillary lymph nodes were enlarged. Purulent nasal discharge was present. The lips were dry and puffy. The gums and tongue were normal. The buccal mucosa was covered by large bullous lesions which were easily ruptured, leaving a purulent exudate on the tongue blade. The pharynx and tonsils were normal. The remainder of the physical examination was negative except for a crusted vaccination lesion.

Laboratory studies: The urine was normal. The hemoglobin was 10 Gm.; red blood cell count, 4,750,000; white blood cell count, 24,800, with 67 per cent neutrophiles of which 10 per cent were nonfilamented, 5 per cent eosinophiles, 1 per cent basophiles, 25 per cent lymphocytes, and 2 per cent monocytes. The Wassermann reaction was negative. The sedimentation rate (Wintrobe method) was 2 mm. per hour, corrected.

The patient remained afebrile and improved rapidly on symptomatic therapy, including vitamins and iron, and was discharged as well on the sixth day of hospitalization.

CASE 2.—L. G., aged 15 months, white, female, entered with the complaint of a sore mouth of one day's duration. Two days before entry the child was fretful and slept poorly. On the following day the child's face became swollen and she refused to eat. On the day of entry, the mother noted bleeding and discharge from the mouth. The child had been vaccinated successfully twelve days before the onset of these symptoms. The child was known to be sensitive to wheat, egg, and orange.

Examination revealed the rectal temperature to be 101° F. The child was fretful and appeared quite ill. A macular and maculovesicular rash was noted generally over the body from the hairline to the ankles. The lesions were small, bronze in color, and of uniform size. On the left arm was a crusted vaccination lesion. The angles of the mouth were fissured and bleeding. The gums were spongy and bled easily when touched. On the buccal mucosa were large, white, sloughing patches which bled on pressure. The pharynx was very injected, but no exudate or membrane was present. The remainder of the physical examination was negative.

Laboratory studies: The urine was normal. The hemoglobin was 16 Gm.; red blood cell count, 5,150,000; white blood cell count, 22,000, with 75 per cent neutrophiles of which 10 per cent were nonfilamented, 2 per cent eosinophiles, and 23 per cent lymphocytes. Smears of the mouth were negative for fusiform bacilli and spirochetes, as were cultures for streptococci and diphtheria. Under treatment with mouthwashes of sodium perborate the lesions cleared rapidly. The child was afebrile in twenty-four hours and was discharged after six days.

CASE 3.—J. B., aged 9 years, white, female, was referred to the hospital with the diagnosis of probable diphtheria. She had been vaccinated for the second time ten days previous to entry. Three days later she developed coryza. Three days afterward sore throat and wheezing appeared. Her physician had prescribed sulfonamide but she had consistently vomited the drug. Two days before entry, eight days after vaccination, her face became puffy and her lips began to swell. The day preceding hospitalization her gums started to bleed and her "mouth started to slough and her breath became foul." The patient developed difficulty in swallowing and marked dyspnea. The latter was relieved by subcutaneous epinephrine. Past history disclosed the occurrence of pertussis and rubella in early childhood, and asthma of several years' duration. She had been vaccinated successfully at 10 months of age.

Examination revealed the rectal temperature to be 104° F. The child appeared acutely and severely ill. On the trunk and extremities were large, red, raised lesions which were entirely discrete but variable in size. A healing vaccination was noted on the left arm. The eyelids were swollen and red and the conjunctivae were markedly injected. In addition, several small subconjunctival hemorrhages were present in the right eye. The breath was foul. The lips were swollen, crusted, and bleeding. Small patches of a grayish membrane were seen over the gums, buccal mucosa, and pharynx. Squeaks and groans were heard throughout both lung fields, but no râles or changes in percussion note were found. The remainder of the physical examination was normal.

Laboratory studies: The urine was normal. The hemoglobin was 94 per cent; red blood cell count, 4,150,000; white blood cell count, 12,000, with 62 per cent neutrophiles of which 2 per cent were nonfilamented, 2 per cent eosinophiles, 36 per cent lymphocytes. The Wassermann reaction was negative.

The patient remained in the San Francisco Hospital for only twenty-four hours, and was then transferred to private care. Inquiry later revealed that she had made a complete recovery.

This patient had a history of sulfonamide ingestion, but had supposedly vomited each dose. Fletcher and Harris[2] report three cases of erythema multiforme possibly caused by sulfonamides. We feel that the sulfonamide probably played no part in this patient's illness.

CASE 4.—F. W., aged 18 years, white, female, developed a sore throat and mouth five days before entry. The following day she felt weak and developed a fever which persisted. The patient had had similar attacks of sore mouth previously and had been told by her physician she was allergic to cats. After giving her cat away she had no further difficulty until the present illness. The day before entry a blister with a red border appeared on her nose. The lesions spread over her face and then the rest of her body. For eight

weeks preceding hospitalization the patient had experienced frequent nosebleeds. Past history revealed that she had had an episode of fever and joint pains at the age of 11 years, but nothing similar since. In addition she had had measles, chickenpox, pertussis, and mumps.

The rectal temperature was 105° F. The patient appeared acutely ill and uncomfortable and exhibited a moderate degree of dyspnea. The conjunctivae were markedly injected. The lids were covered with a discrete rash characterized by a small bleb surrounded by a bright red border. A diffuse eruption was present all over the body, but was most intense on the face. The lesions were vesicles surrounded by a bright red areola. The lips were cracked, oozing purulent material. The entire mucosa of the mouth was covered with a grayish membrane which wiped off easily, leaving a bleeding surface. The gums were purplish with a slight exudate about the margins. The pharynx was covered with the same type of membrane found in the mouth. Coarse, dry rhonchi were heard at both lung bases, and a friction rub was noted at the left base. The heart rate was 140 per minute. The heart was of normal size to percussion. The pulmonic second sound was accentuated. A soft apical systolic murmur was present. The remainder of the physical examination was negative. The clinical impression was acute rheumatic fever with erythema multiforme.

Laboratory investigation revealed the urine to be normal on repeated examinations. The hemoglobin was 14 Gm.; red blood cell count, 4,700,000; white blood cell count, 11,000, with 81 per cent neutrophiles, 1 per cent eosinophiles, 1 per cent basophiles, 13 per cent lymphocytes, and 4 per cent monocytes. Repeated blood counts were gradually nearer normal. The Wassermann reaction was negative. Cultures from the skin lesions failed to grow. Cultures of the sputum revealed hemolytic staphylococcus aureus, streptococcus viridans, and other organisms of the oral flora. The serum albumin was 3.16 Gm. per cent; the globulin 2.14 Gm. per cent. Icterus index was 7.2 units. The nonprotein nitrogen was 45.4 mg. per cent; one week later it had declined to 35.4 mg. per cent. Roentgenologic examination of the chest on entry showed the left border of the heart to be straight, suggesting mitral valve disease. Mottled areas of increased density were present throughout the lung fields. A chest film two weeks later showed a heart of mitral configuration but not enlarged grossly. The lungs were then clear. Serial electrocardiograms were obtained. The initial record, shortly after entry, revealed a sinus tachycardia of 136 per minute. There was slight tendency to right axis deviation. P-R interval was 0.12 seconds. P_2 and P_3 were tall and peaked. T_1 was flat. ST_2 was depressed and T_2 was flat. T_4 was low. Succeeding records showed a gradual reversal until all T-waves were normally upright.

Intravenous phenolsulfonphthalein excretion was 75 per cent in one hour. Arm-to-tongue and arm-to-lung circulation times were 11 and 6 seconds, respectively. Sedimentation rates gradually declined from an initial high level to near normal on discharge to convalescence.

During the first week in the hospital a septic fever reaching as high as 105° F. daily continued, but then declined by lysis. The chest gradually cleared and the patient was discharged after forty days.

CASE 5.—I. F., aged 21 years, white, female, entered with a history of a sore throat of three days' duration and a rash for one day. Except for one episode of vomiting, she had no other symptoms. Past history revealed the occurrence of measles, chickenpox, and pertussis.

Physical examination disclosed the rectal temperature to be 100° F. The throat was very red and a slight amount of exudate was present. A typical scarlatiniform rash was noted, maximal in the skin folds. There was an early "strawberry" tongue. The remainder of the physical examination was negative.

The urine was normal. White blood cell count was 8,400, with 70 per cent neutrophiles. Throat culture revealed nonhemolytic streptococcus.

A Schultz-Charlton test was applied and the area blanched. Seven days after administration of the horse serum used in the blanching test, a number of macular erythematous areas appeared over the extremities. These increased in number the following day,

and redness and swelling of the small joints of the hands and feet were noted. An electrocardiogram was normal. The skin lesions and joint manifestations disappeared in two days and the patient was discharged with the diagnosis of scarlet fever, and erythema multiforme and multiple arthritis due to horse serum.

CASE 6.—F. C., aged 3½ years, white, male, entered San Francisco hospital with a history of cough and coryza of 10 days' duration. Three days before entry the patient developed a fever, and on the day preceding hospitalization a rash appeared on the abdomen and spread rapidly over the body. The past history was irrelevant.

Physical examination revealed an acutely ill child whose rectal temperature was 103° F. Respirations were rapid and the child coughed frequently. A fading maculopapular rash which was hemorrhagic in some areas was present over the face, trunk, and extremities. There were several ulcerated areas on the buccal mucosa, 3 to 4 mm. in size, but no Koplik's spots were noted. The throat was red and considerable purulent postnasal discharge was seen. Crepitant râles were heard throughout both lung fields. The remainder of the physical examination was negative.

Transient acetonuria was the only abnormal urinary finding. The white blood cell count was 25,000, with 56 per cent neutrophiles.

The patient became afebrile in three days following the administration of sulfadiazine. The lesions of the skin and of the mucous membrane cleared. No possible cause for the multiform lesions could be demonstrated at any time.

DISCUSSION

While no definite proof of the etiology of the syndrome of erythema multiforme is available, it seems probable from our data that some allergic phenomenon, or, rather, an antigen-antibody reaction is the cause. Cases 2, 3, and 4 give a past history of allergy. In the instance of the patient discussed in Case 4, who had rheumatic fever, it seems likely that the erythema multiforme was, in common with the carditis, a manifestation of streptococcal sensitivity. The patient of Case 5 had received horse serum and the multiform rash, like the joint manifestations, probably represented serum sickness.

Since the virus is disseminated early in the course of vaccinia, and since toxic absorption might be considered maximal during the stage of pustulation, the late occurrence of postvaccinal erythema multiforme is most compatible with an allergic phenomenon.

In four of our six patients, the mucous membrane lesions of the mouth, and, to a lesser degree, those of the conjunctivae, were so striking and so unlike any other lesions, that they probably can be considered pathognomonic of erythema multiforme.

Three of our patients, Cases 3, 4, and 6, presented chest findings suggestive of a diffuse pneumonitis. Sputum cultures in Case 4 revealed only organisms of the oral flora. It seems likely that this pulmonary process might be due to lesions similar to those seen in the mouth.

SUMMARY

1. Erythema multiforme may occur as an infrequent complication of smallpox vaccination.

2. The occurrence of erythema multiforme following vaccination, horse serum administration, and during rheumatic fever, together with the high inci-

dence (50 per cent) of an allergic history, suggests that the disease represents an allergic reaction.

3. The mouth lesions of this syndrome are so unique as to be diagnostic.
4. Pneumonitis is of frequent occurrence in erythema multiforme.

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A CASE OF ERYTHROBLASTOSIS FETALIS CAUSED BY ISOIMMUNIZATION WITH THE AGGLUTINOGEN B

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ERYTHROBLASTOSIS fetalis is an antigen-antibody disease of the newborn which may occur unrelated to the Rh factor. It may result from the isoimmunization of an Rh-positive, type O mother whose baby is either type A or type B, and a specific increase in the normally present isoagglutinin titer of the mother's blood may be taken as confirmatory evidence of such isoimmunization.

Levine,[1] in an early review of the pathogenesis of erythroblastosis fetalis, stated that the disease is caused by isoimmunization of the mother by a dominant hereditary blood factor in the fetus, which was the Rh factor in more than 90 per cent of the cases. He postulated that the remainder of the cases might be induced by the factor A or B in the fetal blood. More recently, Halperin and associates[2] indicated that such might be the case when the mother was type O and the baby type A. Polayes and Ohlbaum[3] have demonstrated nine cases where the Rh factor as well as the Hr antigen were excluded as possible immunizing antigens and all of the children were type A and their mothers type O, with high anti-A agglutinin titers in the mothers' serum.

To date there have been no reports in the literature of a specific case in which the erythroblastotic infant was type B and the mother Rh-positive, type O, with an elevated anti-B agglutinin titer in the mother's serum. The purpose of this communication is to report such a case.

CASE REPORT

L. B., a 7 pound, 2 ounce full-term, white male, was born Dec. 26, 1945. The infant was apparently normal at birth, but within twenty-four hours was markedly icteric and the liver was enlarged to one and one-half fingerbreadths below the costal margin. Study of the peripheral blood showed the typical findings of erythroblastosis fetalis. Transfusion was temporarily delayed because of the high hemoglobin value and the high red blood cell count, but the following day these findings were lower and the baby had lost 4 ounces. The infant was given a transfusion of 75 c.c. of whole citrated blood. There was a good hematological response to the transfusion and he maintained his weight. It was necessary to give him an additional transfusion on the sixth day of life because of a second fall in the red cell count. (Table I.) He made an uneventful recovery from his erythroblastosis fetalis and was discharged on his eighth day of life. He was only faintly jaundiced and the liver was no longer palpable at that time. The peripheral blood on discharge was that of the normal newborn. He is now alive and is completely normal in every respect.

Complete examination of the blood of the mother, father and baby revealed:

Father: Group B N, Rh-positive, group Rh_1, Hr positive
Baby: Group B N, Rh-positive, group Rh_1, Hr negative
Mother: Group O MN, Rh-positive, group Rh_1

From the Departments of Pediatrics and Pathology, Beth-El Hospital.

Examination of the serum of the mother showed no anti-Rh agglutinins, and no anti-Hr agglutinins. There were no blocking antibodies. The result was negative when tested by the conglutinin method.

The mother's serum, however, showed agglutinins against A_2 cells in titer of 25, and against B cells in titer of 100. When tested by the conglutinin method against A_2 cells the titer was 50, and against B cells the titer was 400.

TABLE I. HEMATOLOGICAL COURSE OF INFANT L. B.

DAY OF LIFE	NUCLEATED RBC PER 100 WBC	HEMOGLOBIN IN GRAMS	ERYTHROCYTES	LEUCOCYTES
1	27	16.0	5,320,000	32,000
2	5	14.0	4,580,000	32,000
3	7	15.0	4,490,000	23,000
4	3	17.5	4,720,000	17,650
5	1	14.5	3,330,000	16,250
6	2	14.0	3,630,000	15,650
7	2	17.5	5,360,000	13,450
8	1	18.0	4,500,000	19,000

SUMMARY

A case of erythroblastosis fetalis caused by isoimmunization of an Rh-positive, type O mother by a type B baby is reported with confirmatory blood serologic findings.

It is suggested that when an erythroblastotic infant is seen, whose mother is type O and her Rh factor is unknown, the baby be transfused with type O, Rh-negative blood. This would obviate the possibility of giving the infant blood to which he has circulating isoagglutinins.

We are indebted to Dr. Lester J. Unger, Director of the Blood Transfusion and Plasma Division of the New York Post-Graduate Medical School and Hospital, for the complete study of the blood of this family.

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TRANSFUSION OF VERY SMALL INFANTS UTILIZING PNEUMATIC PRESSURE

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COMMON difficulties of transfusing tiny infants, such as sticky syringes, intermittent flow, variation of force applied to the plunger, air bubbles getting into the line, and accidental yanking of the needle out of the vein, are obviated by employing air pressure as an impelling force. This arrangement affords all the advantages of gravity with less than a foot of small caliber blood-count-pipette rubber tubing, and using as small calibered needle as desired.

The method can furthermore be employed in infusions by bone-marrow route or otherwise when the rate of flow needs to be accelerated, but at the same time controlled.

A sphygmomanometer is utilized to provide the compressed air. Either mercury or aneroid type will do. By insertion of a Y or T tube in the line from the bulb to the rubber arm cuff, air under any desired degree of pressure may be conducted through a stopper into the top of the blood reservoir, there to exert a continuous, even, controllable force for driving the blood into the vein.

The rate of flow is adjusted by raising or lowering the mercury; 4 to 5 c.c. per minute is best. At this rate, the baby's circulation can accommodate a maximum quantity of blood or saline suspension of cells with a minimum danger of cardiac distention. As much as 15 c.c. of whole blood (or 20 c.c. of saline suspension of cells) per pound of body weight have been given with no reaction.

A 22 gauge needle delivers at this rate most satisfactorily.

The sphygmomanometer may rest on the tray of a Mayo stand, while the blood reservoir and its subjacent filter-drip are suspended from the projecting rim of the same stand (or from a standard close by) at just such a height that two inches of small caliber rubber tubing will connect with a 3-way stopcock on the table, and six inches more tubing leading to a glass observation tube and suitable needle will complete the conducting system to the baby. A 10 or 20 c.c. syringe for saline solution occupies the extra inlet to the 3-way stopcock.

As a blood reservoir I find the barrel of a 100 c.c. syringe, closed with a No. 8 one-hole stopper convenient. Its accurate calibration recommends it particularly. A commercial bottle such as the transfuso-vac can be used, however, by adding, at the base of the Y tube, a rubber tube leading to a needle adapter and a 20 gauge needle which is inserted through a prepared thin spot in the rubber stopper, into the air-admitting glass tube which is part of the apparatus. Steps in the use of the apparatus follow:

1. Fill syringe with saline and attach to 3-way stopcock.
2. Turn stopcock to connect saline syringe with filter-drip, and run saline up the tube and into the bottom of the drip glass to a height of about 3/8 inch.

3. Turn stopcock to connect saline syringe with intravenous needle and run saline through till it drips from the intravenous needle.

4. Pour blood into container and insert cork tightly; (or if the commercial bottle is used, insert air-line needle into its aperture in the stopper).

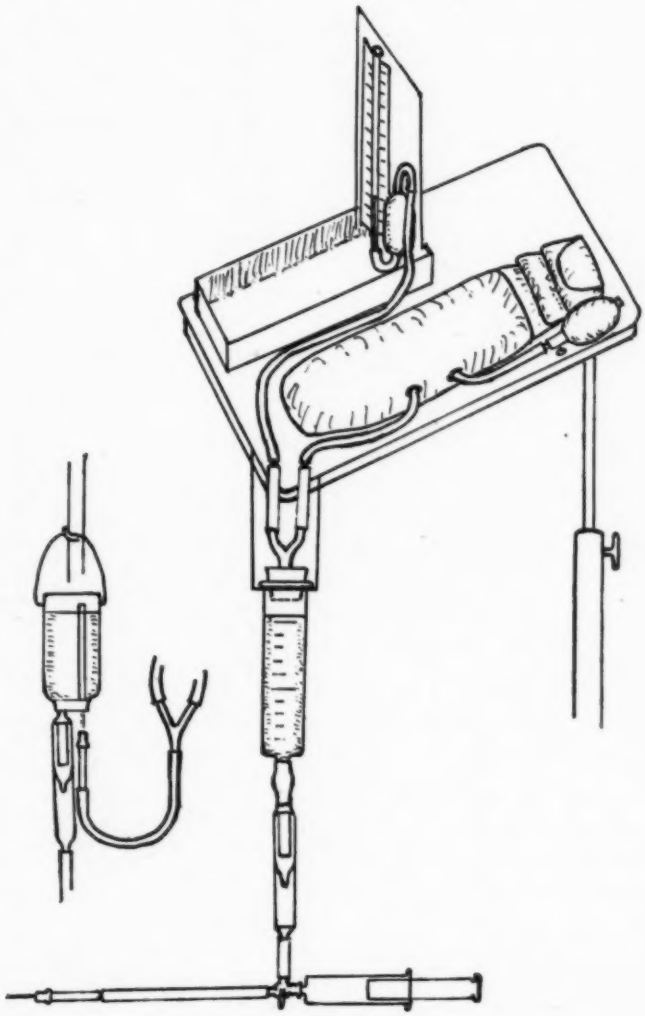

Fig. 1.

5. With sphygmomanometer valve closed, pump pressure up till it reaches and rests at 50 mm.

6. Apply tourniquet.

7. Insert needle in vein, by direct venepuncture if possible—by cut-down and tie-in if necessary.

8. Assure presence of needle in vein by withdrawing slightly on saline syringe.

9. Remove tourniquet.

10. Assure discharge of needle into vein by injecting a few c.c. of saline.

11. Turn stopcock to connect blood with needle.

12. Increase air pressure as necessary till flow is 4 to 5 c.c. per minute, and regulate from time to time to keep flow at this rate. (This has been found to vary according to size of needle used, position in vein, resistance of baby and other factors from 50 mm. up to as high as 120.)

13. Stop the flow not later than when the last drop of blood reaches the observation tube so that air is not blown into the vein.

If trouble develops at the needle:

1. Turn stopcock to stop blood flow and connect saline syringe with needle.

2. Withdraw needle from vein, and insert it in saline solution.

3. With syringe draw saline up through needle till observation tube contains saline instead of blood.

4. Adjust air pressure to 50 mm.

5. Repeat previous procedure beginning at No. 6.

The Academy Study of Child Health Services

THE SECOND YEAR OF THE STUDY BEGINS WITH TWO CAMPAIGNS AHEAD

As the first year of active progress in the Study of Child Health Services draws to a close, the time has come to take stock of the present situation and to outline for members of the Academy the general plan of action for the coming year.

As of September first, state programs have been successfully organized in all but one of the forty-eight states, including the District of Columbia and the Territory of Hawaii. In addition to the original pilot study in North Carolina, five states have completed the data-collection phase of their programs, and several others are rapidly approaching this stage. In the relatively small number of states in which the distribution of the questionnaire schedules has not been completed, it is anticipated that this phase of the Study as well as the collection of the data will be accomplished within the next few months. Thus the end of the calendar year should find this initial phase of the Study complete on a nationwide scale. With the final stages of the state programs in sight, the Central Executive Staff has been developing its activities primarily along two main lines: the statistical analysis of the material gathered in the states and the development of that part of the Study concerned with an evaluation of pediatric education.

STATISTICAL ANALYSIS

In anticipation of the volume and significance of the work now confronting us, the statistical division of the Central Executive Staff has been greatly strengthened. On September 1, Mr. Rollo Britten was appointed a full-time member of the executive staff. Mr. Britten has been giving half time to the Study since June, 1945, dividing his time between the Academy Study and the Commission on Hospital Care. Now, having been relieved of all other responsibilities, he has been appointed by the director and paid from Academy funds in order to take charge of the statistical division of the Study. In view of his many years' service as statistician with the U. S. Public Health Service, and by virtue of his experience as chief analyst of the results of the National Health Survey, Mr. Britten is particularly well qualified for this most important assignment.

One of the aspects of the statistical work which is now receiving increased emphasis is the reviewing, correcting, and, in so far as is possible, completing of the information requested on the questionnaire schedules. No matter how strong the statistical team at the Central Office, the value of the results will be limited by the diligence and accuracy with which these data are collected and reported by the state executive secretaries. To supervise this work and to assist the executive secretaries in this important aspect of the Study, Mrs. Mary Hubbard was added to the central staff in August. Mrs. Hubbard's first activity as a staff member will take her on tours throughout the states in order that she may assist the executive secretaries in giving maximum value to the completed questionnaires before they are sent in to the Central Office.

As the statistical division of the Study staff is growing rapidly, a greatly expanded office is planned to accommodate the increase in personnel required. In order to accomplish the tremendous amount of statistical labor within the shortest possible time, it is expected that an additional fifty or sixty full-time editors and coders will be needed during the coming winter. Supervision of the technical force will be in the hands of Miss Regina Lowenstein, another newcomer to the staff, who has had extensive statistical experience.

In the August issue of the JOURNAL OF PEDIATRICS, this column contained a description of preliminary plans for three regional meetings to be held during September in Chicago, San Francisco, and Washington. These meetings have grown out of the fact that state chairmen have expressed to us in the Central Office their feeling of a need to discuss with the

executive staff the question: What are the states going to get out of this Study? State chairmen, executive secretaries, and state committees have put so much effective effort, time, and money into collecting the desired information that increased emphasis has been given to the importance of suitable reports to be written for each State. It has appeared essential, therefore, to provide, as soon as possible, an opportunity for the executive staff to obtain from state groups a more definite and detailed expression of their opinions, and at the same time to give to these state groups some idea of the statistical limitations of the Study, together with a description of the tabulations now being prepared. For this purpose a first draft of an outline covering the main topics to be included in reports of the Study at both national and state levels has been drawn up for presentation and discussion at the meetings. Questions pertaining to each of the major topics are included in the outline and the tentative analytical table forms to be used in answering the proposed questions will also be presented. Judging from the enthusiastic response with which the original plan for these three meetings was received, all three sessions promise to produce spirited discussion and exchanges of opinion. Copies of the outline have been distributed to all persons planning to attend the meetings, in order that they may be prepared to make suggestions, additions, and other pertinent comments concerning the proposed content of the state reports. After these meetings have taken place, a full report of them will be presented in the November issue of the JOURNAL OF PEDIATRICS.

STUDY OF PEDIATRIC EDUCATION

This important phase of the Study concerning the character and scope of pediatric training in medical schools and teaching hospitals is to be conducted during the academic year 1946-1947. By this time it is anticipated that medical school curricula will have returned sufficiently to normal to permit a fair evaluation of pediatric education. Plans for this portion of the Study have been developed gradually during the past winter and summer and will be put into operation at an early date.

Dr. James L. Wilson, Professor of Pediatrics of the University of Michigan, has been appointed chairman of the subcommittee under whose direction the study of pediatric education is to be conducted. This committee is made up entirely of professors of pediatrics and chiefs of pediatric departments chosen from various sections of the country so that each member of the committee can be responsible for an area including approximately ten medical schools, thus covering all sixty-eight medical schools in the U. S. A. The members of this committee and the medical schools assigned to them are as follows:

DR. JAMES L. WILSON, Chairman. Professor of Pediatrics, University of Michigan Medical School.

MEDICAL SCHOOLS

Wayne University College of Medicine, Detroit, Mich.
University of Michigan, Ann Arbor, Mich.
Western Reserve University School of Medicine, Cleveland, Ohio
University of Buffalo School of Medicine, Buffalo, N. Y.
University Rochester School of Medicine, Rochester, N. Y.
Syracuse University College of Medicine, Syracuse, N. Y.
University of Pittsburgh School of Medicine, Pittsburgh, Pa.
Ohio State University College of Medicine, Columbus, Ohio
University of Cincinnati College of Medicine, Cincinnati, Ohio
University of Louisville, Louisville, Ky.
Indiana University School of Medicine, Indianapolis, Ind.

DR. HENRY G. PONCHER. Professor of Pediatrics, University of Illinois College of Medicine.

MEDICAL SCHOOLS

Loyola University School of Medicine, Chicago, Ill.
Northwestern University Medical School, Chicago, Ill.
University of Chicago School of Medicine, Chicago, Ill.

University of Illinois College of Medicine, Chicago, Ill.
University of Wisconsin Medical School, Madison, Wis.
Marquette University School of Medicine, Milwaukee, Wis.
University of Minnesota Medical School, Minneapolis, Minn.
State University of Iowa College of Medicine, Iowa City, Iowa
St. Louis University School of Medicine, St. Louis, Mo.
Washington University School of Medicine, St. Louis, Mo.
University of Kansas School of Medicine, Kansas City, Kan.
Creighton University School of Medicine, Omaha, Neb.
University of Nebraska College of Medicine, Omaha, Neb.

DR. SAMUEL LEVINE. Professor of Pediatrics, The Cornell University College of Medicine.

MEDICAL SCHOOLS

Yale University of Medicine, New Haven, Conn.
Columbia University, New York, N. Y.
Cornell University, Ithaca, N. Y.
New York Medical College, New York, N. Y.
New York University College of Medicine, New York, N. Y.
Long Island College of Medicine, Brooklyn, N. Y.
Boston University School of Medicine, Boston, Mass.
Harvard Medical School, Boston, Mass.
Tufts College Medical School, Boston, Mass.

DR. RALPH V. PLATOU. Head of Department of Pediatrics, Tulane University of Louisiana, School of Medicine.

MEDICAL SCHOOLS

Southwestern Medical College, Dallas, Texas
Baylor University College of Medicine, Houston, Texas
University of Texas School of Medicine, Galveston, Texas
University of Oklahoma School of Medicine, Oklahoma City, Okla.
Louisiana State University School of Medicine, New Orleans, La.
Tulane University School of Medicine, New Orleans, La.
University of Arkansas School of Medicine, Little Rock, Ark.
University of Tennessee College of Medicine, Memphis, Tenn.

DR. ROBERT LAWSON. Assistant Professor of Pediatrics, Bowman Gray School of Medicine of Wake Forest College.

MEDICAL SCHOOLS

Meharry Medical College, Nashville, Tenn.
Vanderbilt University School of Medicine, Nashville, Tenn.
University of Virginia Department of Medicine, Charlottsville, Va.
Medical College of Virginia, Richmond, Va.
Duke University College of Medicine, Durham, N. C.
Bowman Gray School of Medicine, Winston-Salem, N. C.
Medical College of the State of South Carolina, Charleston, S. C.
Emory University School of Medicine, Atlanta, Ga.
University of Georgia School of Medicine, Augusta, Ga.

DR. FRANCIS SMYTH. Dean, University of California Medical School.

MEDICAL SCHOOLS

University of Oregon Medical School, Portland, Ore.
University of California Medical School, San Francisco, Calif.
Stanford University School of Medicine, San Francisco, Calif.

College of Medical Evangelists, Los Angeles, Calif.
University of Southern California School of Medicine, Los Angeles, Calif.
University of Utah School of Medicine, Salt Lake City, Utah
University of Colorado School of Medicine, Denver, Colo.

DR. WALDO NELSON. Professor of Pediatrics, Temple University School of Medicine.

MEDICAL SCHOOLS

Hahnemann Medical College, Philadelphia, Pa.
Jefferson Medical College of Philadelphia, Philadelphia, Pa.
Temple University School of Medicine, Philadelphia, Pa.
University of Pennsylvania School of Medicine, Philadelphia, Pa.
Woman's Medical College of Pennsylvania, Philadelphia, Pa.
John Hopkins University School of Medicine, Baltimore, Md.
University of Maryland School of Medicine, Baltimore, Md.
Georgetown University School of Medicine, Washington, D. C.
George Washington University School of Medicine, Washington, D. C.
Howard University College of Medicine, Washington, D. C.

A preliminary meeting of this committee was held in Washington, D. C., in June of this year at which time the first draft of the questionnaire schedules for this portion of the Study (Series IV) and the general plan of action were discussed. It was agreed that, in so far as circumstances allow, a visit should be made by the committee members to each medical school assigned to them together with one or more members of our Central Executive Staff. In this way the study of each school could include the opinions of an outstanding teacher of pediatrics plus those of a member of our staff whose past experience includes both practice and teaching and whose function would be to assure that in each school the same techniques of gathering information are used. In this manner a consistent and most interesting picture of pediatric education throughout the country should be obtained. Dr. John McKenney Mitchell has been designated as the member of the Central Executive Staff to serve as full-time director of this part of the Study. It may be that Dr. Mitchell will not be able to visit all of the medical schools during the coming year in which case other members of the executive staff will visit some of the schools and teaching hospitals.

JOHN P. HUBBARD, M.D.,
Director, Study of Child Health Services

The Social Aspects of Medicine

COMPULSORY PREPAID MEDICAL CARE*

By W. A. Milliman, Second Vice President

The Equitable Life Assurance Society

By the very nature of things there can be no precise and final division between governmental and private responsibilities for national health. These relationships are constantly changing and in recent years there have been remarkable advances in the science of medicine. These advances have been possible because there existed a spirit of initiative and freedom for experimentation. There is constant danger that, as governmental responsibilities are extended, inflexible patterns will be established, either by law or regulation, which will dampen the spirit of initiative and handicap experimentation. Consequently, whatever changes in the relationships between governmental and private responsibilities may be made in the future, it is of the utmost importance that we preserve these characteristics of the system of private enterprise.

PUBLIC VS. PRIVATE RESPONSIBILITY

It is clear that government has primary responsibility with respect to certain activities essential to the health of the nation which, if they are to be performed effectively, must be handled by concerted action on the part of the community. On the other hand, the health and well-being of the individual is affected by a multitude of decisions and actions which are, and must necessarily be, the responsibility of the individual. Since the health of the nation must be measured in terms of the health of its individual citizens, many of the essentials of national health must remain in the domain of private responsibilities.

It is primarily in this field of joint responsibilities that there is disagreement as to the proper nature and extent of governmental participation. Specifically, there is sharp disagreement with respect to the nature of the responsibility which government should assume for the provision of medical, hospital and dental care for the self-supporting citizen and the extent to which government should assume responsibility for the continuation of the worker's income during periods of disability.†

CRITICISM OF PRESENT SYSTEM

What do the proponents of compulsory health insurance seek to accomplish in this field of medical care? Their objectives seem to be concerned with the kind and the quality of medical care which the American public is now getting as well as with the cost of this medical care. It is claimed that not enough emphasis is placed on preventive care, that we do not have adequate facilities and personnel available for good medical care for all of the people, and that the facilities and personnel which we now have are not ideally distributed nor efficiently utilized. As to cost, it is claimed that good medical care is beyond the financial capacity of the majority of our citizens and that in any event these costs, because of their unpredictable incidence, frequently constitute financial catastrophes to the individuals who must pay the bills.

Much of this is true. The important question is, will the proposals for compulsory health insurance, such as those contained in the Wagner-Murray-Dingell Bills, S. 1606 and H. R. 4730, improve the situation? Many serious students of these problems have grave doubts on this point. Important among the reasons for these doubts are the following:

In the first place it is certain that many controls would be necessary both as to the manner in which the medical practitioners could practice their professions and as to the condi-

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†The latter will be treated by the author in a subsequent article.

tions under which eligible persons could avail themselves of medical services. These controls would probably be of such far-reaching character that they would result in unforeseen changes in the present bases of the practice of medicine. There has not been sufficient discussion of the necessity, under a plan of compulsory health insurance, for such controls, nor has adequate consideration been given to their probable consequences. While the proponents of compulsory health insurance have apparently given some consideration to these problems, they have not been frank with regard to these points with either the medical profession or the public.

CRITICISMS EXAMINED

As a result it is doubtful whether members of the medical profession would willingly participate in a plan of compulsory health insurance in sufficient numbers to enable it to achieve its objectives. Even if all of the present members of the medical profession should participate in and fully cooperate with the plan there are not enough doctors, dentists and nurses available to give the public the quality of care which it is entitled to expect and at the same time to furnish the amount of care which would be demanded if the factor of private financial responsibility were entirely removed.

President Truman and the Social Security Board have recommended that the Social Security Act be amended to include provision for medical care benefits. Senators Wagner and Murray, together with Representative Dingell, have, with the obvious approval of both the President and the Social Security Board, submitted to Congress a bill which would, among other things, provide such benefits. The remarks which follow will be based on the provisions of Title II of this bill relating to "prepaid personal health service benefits."

DIFFICULTIES UNDER COMPULSORY SYSTEM

Substantially the entire population of this country including both employees and their dependents would, under the terms of this bill, be entitled to medical, dental, nursing, laboratory and hospitalization benefits, subject to certain limitations. The cost of these benefits would, presumably, be met by a payroll tax upon both employers and employees. Responsibility for administration of this plan would be placed in the hands of the Surgeon General under the supervision and direction of the Federal Security Administrator. Provision is made for the establishment of an Advisory Council, appointed by the Surgeon General with the approval of the Federal Security Administrator. As its title indicates, the powers of this Council would be purely advisory.

The bill contains little specific detail as to administrative rules. Responsibility with accompanying broad authority would be vested in the Surgeon General to carry out the purposes of the bill in accordance with certain broad policies outlined in it. Because of the generality of these policies and the wide range of discretion given to these officials it is not possible to conclude from the bill alone what changes in the present system of medicine probably would result if this proposal became law.

It is, however, certain that a national health program such as proposed would cost a great deal of money. It is suggested that this cost would not be materially greater than the price now being paid by the American people for health care. Whether or not this is true the Surgeon General would have to keep the cost of the program within the limitations imposed by the revenues available. If abuses developed, abuses which cost money and threatened the solvency of the program, the Surgeon General would be forced to take steps to cure those abuses, or to limit their financial effect. Whether he seeks to cure the abuses by regulations limiting the conditions under which an individual can obtain medical service or regulations restricting or prohibiting certain medical practices, or whether he seeks to limit the financial effect of abuses by changing the basis of compensation of physicians and dentists, these regulations can, and probably would, fundamentally alter many features of the present system of medicine and medical economics.

The avowed purpose of the bill is to give everyone ready access to good medical care. The Surgeon General must, therefore, obtain the participation and the cooperation of the medical professions. Without that participation and cooperation, including that of the

more competent members of these professions, the plan would be an empty gesture. Whatever the justification for their attitude, the violent reaction of the organizations representing the major portion of the medical professions would indicate that such cooperation cannot be achieved at this time. Nor does it seem likely that their cooperation can be obtained in the future if there is a continuation of the lack of candor which has so far characterized the proponents of this type of legislation. The sort of cooperation which is necessary cannot be obtained by compulsion. If there is a reasonable basis for cooperation, obviously it can be best attained by a full and frank exploration of the necessary readjustments in the present system of medical care with such exploration made jointly by the advocates of such legislation and representatives of the moderate and conservative elements of the medical professions.

If the purposes of the bill are to be carried out more hospitals must be constructed and more doctors, dentists, nurses and technicians must be trained. President Truman has recommended financial assistance to the various States for the construction of more hospitals, and legislative proposals for this purpose are being given favorable consideration by Congress. But as the President pointed out, the building of additional facilities will not provide service. Service can be provided only by competent, well trained personnel. The training of such personnel will take both money and time. But, most important, it will take an adequate supply of competent young people willing to enter these professions. The effectiveness of any program to train more medical personnel will be affected by the attractiveness of these professions to the young people of our country from whom future doctors, dentists and nurses must be recruited.

Because it affects the attitude of the present members of these professions and the attitude of the potential future members, a most vital part of the program is the basis upon which those who render the service required under it will be compensated. The bill provides that the basis of compensation for general practitioners and dentists shall be determined by the majority of such practitioners in each local area with the right reserved to the Surgeon General to use a different basis of compensation for those who do not elect with the majority. It is well known that the majority of physicians in private practice today wish to continue the traditional fee-for-service basis of compensation for their services. It is with respect to this point particularly that the proponents of compulsory health insurance have lacked candor in dealing with the medical profession. While the bill provides that the doctors of any area may elect to continue to be paid on a fee-for-service basis, the principal proponents of this type of legislation, in a statement entitled "Principles of a Nation-Wide Health Program" published in November 1944, stated that:

> "The fee-for-service method is most open to abuse by patients and physicians and is the most costly to administer. Adequate control of the services requires fiscal and professional supervision, which is expensive and often vexatious. The promotion of quality and of prevention is difficult. The use of the fee-for-service method should therefore be discouraged, except for specialist services under certain conditions."

What would be the result, then, if the Surgeon General must permit the doctors of each local area to choose a method of compensation which experts in the field agree will not work, and it appears that a majority of doctors will choose that method? One of the first steps might be to reduce the rate of payment for each unit of service so as to bring the over-all cost of services within the available funds. To reduce the pay of conscientious and competent physicians because of abuses by patients and by less conscientious physicians would be intolerable. The conscientious doctor, if he is to receive the compensation to which he is entitled, would be forced to make unnecessary visits and adopt many other undesirable practices followed by the physician who has abused the system. There would result an application of Gresham's law to the field of medical practices, with the bad driving out the good.

The next step might well be the abandonment of the fee-for-service method as a basis of payment to the general practitioner. The alternative bases of compensation contemplated

by the bill are payment to the general practitioner of a stipulated amount each year for each of his patients, the so-called capitation basis, or payment for the physician's services on a salary basis. These are, by and large, methods untried in this country in the field of general medical care. What effect they would have on the quality of medical care, its cost, and the attractiveness of the field of medicine to the present and the potential future doctors, dentists and nurses is practically unknown.

It might be observed, however, that the capitation method, under which the physician is paid the same amount each year regardless of the work he performs, opens at least two avenues for substantial abuse. In the first place it would be to the financial advantage of the individual physician to avoid taking patients who are apt to require a substantial amount of medical care. There are many ways in which the physician could select his patients for this purpose, and apparently he would be free to do so since the bill would permit the physician to reject individual patients. In the second place the general practitioner would find himself able to handle more patients, and hence to increase his income, if he made a habit of referring patients to specialists as soon as some minor complication arose. Other serious abuses are possible. Whether these abuses would become realities, or would prove to be purely imaginary, can more properly be determined by experimentation with voluntary plans rather than by adoption of a nation-wide compulsory plan.

What would be the result if a salary basis of compensating physicians were substituted for our present fee-for-service basis? Would professional standards be higher or lower than at present? Would the net change in the picture, including the introduction of political and bureaucratic forces, make the medical professions more or less attractive to qualified potential entrants into these professions? The recent disclosures concerning the medical care provided through the Veterans' Administration is disquieting in this connection. Certainly a careful examination of the character and quality of the services which are now being supplied by physicians employed on a salaried basis, including an investigation of the reasons for any shortcomings in the quality of that service, should be made before seriously considering adopting a national system which may force this as a general basis of compensation of physicians.

We have considered briefly the steps which might be taken for the purpose of limiting the financial effect of abuses by changes in the method of compensating physicians and other practitioners. Instead of attempting to limit the financial effect of abuses, the Surgeon General might attempt to avoid abuses by limiting the conditions under which an individual could avail himself of the services of a physician, dentist or hospital, or by restricting or prohibiting certain types of practices by physicians, dentists and hospitals.

Let us take a simple case by way of illustration. The Surgeon General might find that some physicians being reimbursed on a fee-for-service basis were making four, five or six visits for treatment of common colds where one visit would have been sufficient. In order to reduce the financial burden of this type of abuse he might decide that in any case diagnosed as a common cold the physician would not be allowed payment for more than two visits without specific approval of the case by a medical administrative officer. Obviously, it would be a simple matter to circumvent such a restriction by changing the diagnosis. Consequently, if the necessity for such restrictions and regulations should arise in practice, the variety of diseases and the diversity of medical practices would inevitably lead to a formidable volume of rules, regulations and report forms. Serious consideration should be given to the effect of such procedural problems on the ability of the physician to practice medicine efficiently and effectively.

The controls over the individual physician paid on a fee-for-service basis would arise from the necessity of the Surgeon General to limit costs. Use of a capitation basis or a salary basis has been suggested in order to avoid the problems of the fee-for-service basis. While these bases of compensation would be effective in limiting costs it is not clear that they would be effective in maintaining quality of medical care. Consequently, the controls which would be required under a salary basis or a capitation basis would probably be concerned with the problem of trying to assure a high quality of care, and would probably do so by detailed

regulations as to the precise manner in which the physician should practice medicine. Such a development would be accompanied by the grave danger that, by placing an administrative stamp of approval on currently accepted methods of treatment, new techniques and methods of treatment would be difficult to adopt, and might, in fact, be strangled by administrative red tape.

In addition to attempting to control abuses by adopting new methods of compensation, or by regulating the methods of practice by physicians, dentists and hospitals, the Surgeon General might have to limit the services which would be available under the proposed system. Such limitations are specifically contemplated by the Wagner-Murray-Dingell Bill. For instance it is obviously impossible for available personnel to furnish complete dental services to the entire population. Accordingly, the Surgeon General would be permitted to restrict the dental services to examination, diagnosis, prophylaxis, extraction and treatment of acute diseases of the teeth. Home nursing service and laboratory benefits might likewise be limited, because of restricted personnel and in order to control costs. In addition the Surgeon General would be authorized to require the payment of a fee with respect to the first service from a physician, dentist or nurse, or with respect to each service in a period of sickness or course of treatment.

One of the main objectives of those who propose compulsory health insurance is to obtain greater emphasis on preventive medical care. The Wagner-Murray-Dingell Bill recognizes, however, that sheer lack of available personnel, coupled with possible lack of funds, will limit that emphasis, and that abuses may arise which will necessitate barriers to such care. If our available personnel is limited, is it not possible that the abuses which will develop will divert the time and talents of that personnel to such an extent that less rather than more emphasis will be put on preventive care?

CONCLUSION

This suggests the thought that more progress in improving preventive medical care could be made by further emphasizing medical research, by improving facilities for medical education, and by expanding and improving our public health services than would result from adoption of such a far-reaching and apparently unworkable plan as that contained in the Wagner-Murray-Dingell Bill.

There is need for the development of diagnostic centers. Such centers could be developed locally in association with hospitals, or otherwise, to make available on an efficient and economical basis the medical tools and knowledge already developed. These centers should be developed so as to supplement, not replace, the private medical practitioner. They could be financed in part by public funds or by private gifts and endowments, and in part by charges for services.

There is need for further development and experimentation with voluntary plans for prepayment of the costs of medical and hospital care. This development can be aided by the adoption of a more constructive attitude by the medical profession, by the insurance industry, and by employers. It is not suggested that the physician sacrifice those principles which he considers fundamental to the practice of good medical care, but there is room for him to adopt a more constructive and aggressive approach to the solution of the problems of the high cost of medical care. The individual physician should participate in the development of prepayment plans and should educate his patients to take advantage of prepayment plans.

There should be more experimentation with group practice as a foundation for plans for prepayment of medical costs. The individual physician should tolerate, even though he does not participate in, the development of such plans of group practice if they maintain proper medical standards.

Academy News and Notes

The following Fellows of the Academy have been discharged from the service:

Army

Henry L. Barnett, New York, N. Y.
Samuel S. Bernstein, Detroit, Mich.
Charles W. Cory, Saginaw, Mich.
Arthur J. Cramer, Jr., Buffalo (Kenmore), N. Y.
Norman T. Crane, Plainfield, N. J.
William V. B. Deering, Quincy, Ill.
Frank H. Douglass, Seattle, Wash.
S. Butler Grimes, Jr., Baltimore, Md.
Ng William Hing, Puerto Rico
Maurice W. Laufer, Riverside, R. I.
Irving Le Bell, New York, N. Y.
Newell L. Moore, Santa Ana, Calif.
Marsh W. Poole, Klamath Falls, Oregon
Irving Rosenbaum, Jr., Indianapolis, Ind.
James B. Snow, Oklahoma City, Okla.
Irwin P. Sobel, New York, N. Y.
Martin L. Stein, Great Neck, N. Y.
Maxwell Stillerman, Great Neck, N. Y.
Joe M. Strayhorn, Nashville, Tenn.
Hugh C. Thompson, Jr., Tucson, Ariz.

Navy

Otto E. Billo, New York, N. Y.
John H. Doval, Sacramento, Calif.
Benjamin F. Feingold, Los Angeles, Calif.
Herbert William Fink, Norfolk, Va.
Robert N. Ganz, Boston, Mass.
Robert S. McKean, Boise, Idaho
Joseph F. Raffetto, Manasquan, N. J.
Frederick P. Rogers, West Hartford, Conn.
Edward A. Wishropp, Grosse Pointe Farms, Mich.

Canadian Navy

Harry L. Bacal, Montreal, Quebec, Canada

Lt. Herbert William Fink has been promoted from Lieutenant (j.g.) to Lieutenant in the Navy.

Dr. Stanley D. Giffen, Toledo, Ohio, died on May 5, 1946. He was an Emeritus Member.

Book Reviews

Government in Public Health. Harry S. Mustard, M.D., LL.D., New York, 1945, The Commonwealth Fund, 219 pages. Price $1.50.

This is an extremely interesting, authoritative, clearly written document which treats of contemporary public health work as a historical product. This approach, although it gives the social and political aspects of the subject rather than the scientific, the national aspects rather than the local, the general rather than the specific, enables one to view the present situation as a transition or trend.

Dr. Mustard points out that those preoccupied with public health organization and administration will not be satisfied with this approach; and he warns anyone who limits his knowledge of public health in the United States to what can be learned from this document that his information will be incomplete and that he will fail to "appreciate the fact that public health work in the United States is of a rather high order qualitatively." This reviewer believes, however, that no one could fail to benefit from this clear, concise presentation of so important a subject at this critical time.

The reader is introduced to the subject by an exposition of certain preliminary considerations such as the biologic and sociologic factors in health and disease, the character of public health problems, factors that express the seriousness of public health problems, factors that determine the make-up of a public health program.

Following these considerations, sixty-two pages are devoted to a discussion of the development of Federal Health Services. Of particular interest is the fact that Federal health work in the United States is not established as a coordinated health unit. In addition to the U. S. Public Health Service, about forty other Federal agencies participate to some degree in public health or medical care activities. Foremost of these are the Department of Agriculture, the Department of Commerce, the Department of the Interior, Federal Security Agency, and the Department of Labor.

As indicated before, emphasis is given to the social and political aspects of the development of the U. S. Public Health Service from the act of 1798, which provided compulsory health insurance for seamen, up to the present time. Throughout this discussion the actual phraseology used by members of the Congress relative to health organization is presented.

The following two chapters are devoted to the development, organization, expenditures, and source of funds of State and local health departments, with constant recognition of the fact that the bulk of actual health service is and must be rendered by local departments of health. It is emphasized that although each of the forty-eight states received some Federal assistance for health purposes, there remains about 25 per cent of the total population of the United States which does not come under the jurisdiction of organized local departments of health. The growth of local health work is indicated by the fact that in 1915 only fifteen counties in the United States were served by organized local health departments, whereas in 1942, 1,828 of the 3,070 counties were so served. For those not aware of the usual activities in a public health program, the chapter on this subject will be very enlightening and should serve as an excellent introduction to further reading.

The last chapter is a brief one relating to a "summary of trends and a consideration of certain needs." This is a well-written, authoritative, critical review of government in public health. It is highly recommended to anyone interested in health, either officially or unofficially. Each chapter is replete with references and documentation of statements made by the author. Several historical documents are reproduced, and there is a satisfactory index.

E. G. C.

American Medical Practice in the Perspectives of a Century. Bernhard J. Stern, Ph.D., New York, 1945, The Commonwealth Fund, 172 pages. Price $1.50.

This is the first of a series of studies undertaken by the Committee on Medicine and the Changing Order of the New York Academy of Medicine to review the problems which now confront the medical profession and to serve as a background to assist in their solution. The author of this document is a lecturer in Sociology at Columbia University and visiting Professor of Sociology at Yale. He has had wide experience, has given much thought to sociology and medical progress, and has written frequently about both subjects.

At the outset the author presents data which demonstrates how the United States changed from an agricultural to an industrial economy and from a rural to an urban society and shows that these changes have "embraced all aspects of human relationships."

In the succeeding six chapters the author freely uses information he himself has gathered, information from the National Health Survey, reports of the Committee on the Cost of Medical Care, U. S. Public Health Service reports, and reports of the National Resources Committee to review again the subjects that are being put before us both in medical and lay journals from time to time—the expanding horizons of medicine, the specialist and the general practitioner, the supply and distribution of physicians, the patient load in medical practice, the income of physicians, and the distribution of medical services.

The book presents a brief summary of these points, and there is a list of some 200 references for those who would search for additional information. Just how valuable a contribution this document proves to be will depend upon how widely the book is read. This reviewer suspects the distribution will be primarily among those who have already informed themselves about these matters. Those who have not will probably continue to get their information by hearsay.

The book is recommended for those who wish to inform themselves by means of a brief review of these subjects, and who would like to be provided with a good list of references for further reading.

E. G. C.

A Future for Preventive Medicine. Edward J. Stieglitz, M.D., F.A.C.P., New York, 1945, The Commonwealth Fund, 73 pages. Price $1.00.

There are many who will agree with the author's statement that "the recent approaches to preventive medicine can be divided into two major fields: (1) control of the environment to render it relatively innocuous, and (2) the improvement of the resistance of individuals who may be exposed to deleterious environmental influences." However, there is another major field in the approach to preventive medicine which many observers will add, and indeed one which is discussed in one form or another by the author throughout the book; detection of disease process early enough for interruption in favor of the individual.

The outstanding theme of the book throughout its sixty-eight pages is that health is a privilege and not a right; that it cannot be given to an individual by medical science or by government, but that it must be earned through the efforts of the individuals themselves with the assistance of those who are competent to help, the physicians themselves.

Much has been accomplished over the years in the prevention of illness by control of environment, but "modern sanitary facilities have been popular because they offered convenience and physical comfort, not because they offered greater safety to health." Until the attitude that health is an inalienable right is abandoned; so long as every illness is considered an intrusion beyond the control of the individual; and until attention is focused upon men, women, and children, who may become ill, rather than upon disease, very little will be accomplished in constructive health.

After a discussion of the accomplishments of preventive and curative medicine in a chapter entitled, "Health Over the Last Forty Years," in terms of the changes in the age structure of the population, changes in mortality, and changes in morbidity, the author presents a program of preventive medicine. Although he points out that in the selection of

the title, "A Future for Preventive Medicine," he deliberately chose the indefinite article "a" rather than the definite article "the" because there are other possible futures, it is evident that he feels strongly that the program presented is *the* most logical and fruitful approach to preventive medicine in the future. He makes a strong case for his ideas, and although there are many who will not agree with everything that is said, everyone will be stimulated by his provocative statements.

In addition to a plea for the continuance of public health activities which have to do primarily with mass measures to minimize health hazards, he insists that private health efforts concerned directly with the individual must be given greater attention than ever before. There must be research and education. "Physicians everywhere must cease shirking their educational responsibilities."

Other physicians can follow the lead of pediatricians in constructive medicine. "Well Adult Clinics," with individualized constructive medicine for adults, should be possible if the population can be shown that the maintenance of health is its own responsibility. The economic difficulties engendered by such a plan are dismissed in too few words.

According to Dr. Stieglitz, the measurement of health, although difficult, expensive, and time-consuming, is the foundation of personal preventive medicine. This is accomplished by the "periodic health inventory" (rather than the term periodic examination), the objectives being (1) the evaluation of health by diagnostic study, which should include measurement of reserve capacity, (2) early detection of insidious disorders in their incipiency, (3) detection and correction of minor but potentially detrimental defects, (4) analysis of habits of living, and (5) direct personalized health education.

This is a very interesting and enlightening book, written by a man who has given considerable thought to the matter. The concept of preventive medicine presented is the modern one and corresponds closely with the ideas of many interested in this particular field. The book is recommended very highly for physicians and medical students. There is an excellent list of sixty-seven references.

E. G. C.

Medical Education and the Changing Order. Raymond B. Allen, M.D., Ph.D., New York, 1946, The Commonwealth Fund, 142 pages. Price $1.50.

This monograph, by the dean of the College of Medicine of the University of Illinois and president-elect of the University of Washington, is one of the series being issued under the auspices of the Committee on Medicine and the Changing Order of the New York Academy of Medicine. As an exposition of the philosophy of one of the more thoughtful leaders in medical education, it deserves a careful reading by everyone interested in medical education and practice. Regardless of whatever changes may evolve in the social and economic phases of the practice of medicine, medical care in the final analysis depends upon the character and quality of medical education. This basic truth has been all too frequently disregarded in the rather hectic discussions of medical organization and economics which have been taking place in recent years.

Dean Allen's underlying theme is that medical education in its development and changes has reflected in large part the social, industrial, and cultural status of the particular period. He says that in the present period, technological progress has outpassed social development in all phases of living, and medical education and practice must meet the changing order. He is not pessimistic, but realizes the challenge of the times.

"Tomorrow's world has the power and resources to meet man's every need. Whether man has the wisdom, humility, and social consciousness to use his new-found powers for the constructive purposes of all mankind is the most important question of our times. The free men of democracy have proved that democracy has the inherent strength to be victorious in a world at war; they have yet to prove that they can win a durable peace. Never before has the spiritual and moral life of man faced a test of this portent for good or evil." (p. 136.)

Turning to the more direct matter of medical education, the author finds that it has been so occupied with the tremendous technological advances of the last few decades that it has neglected to prepare the doctor to fill a broader role as a responsible leader in the

community. This implies a thorough understanding of "the social, industrial, and economic patterns of which he is a part." Preventive medicine should be increasingly stressed in the education of the physician, not simply specific preventive technique and public health, but the "basic environmental conditions in the home, school, factory, and office which make for healthful living or its opposite."

The author suggests no specific changes in the practice of medicine as a cure for the unequal distribution of medical care and the economic problems of the cost of adequate medical care for all. His own viewpoint toward these matters can be summed up by another quotation:

"Physicians of the future must be capable of taking their places as responsible leaders in the community and of viewing the problems of medical service dispassionately. Unless they recognize the right of every person to adequate medical service, the medical profession will degenerate to the level of a trade in which, as tradesmen, physicians will be concerned merely with the technique of their trade. The medical profession cannot assume full responsibility for supplying complete medical service everywhere; it is no more responsible for the inadequacy of medical service in certain economically depressed regions of the country than teachers are responsible for the high illiteracy rates which are often found in the same places. It is under obligation, however, to cooperate fully with voluntary and public agencies so that together they may create the economic and social conditions which make possible an adequate medical service for all."

More specific ideas as to medical education, which, in a sense, are an appendage to the author's philosophy of education in general and the role of the physician, are as follows: (1) He looks for a better, more cultured type of medical student—an expression undoubtedly of his experience as a dean. (2) He feels that teaching ability should have more recognition in the selection of the medical faculty—an opinion held by many medical students. (3) He raises the question as to the sharp departmental lines under which nearly all of our medical school faculties are organized, and as to whether this is consistent with "the trend toward unity which is developing within the medical sciences themselves." (4) He urges that the faculties of our medical schools accept their responsibilities at the faculty rather than the departmental level. These are only a few of the points and suggestions expressed by the author.

It is a most thought-producing monograph, which unquestionably will not only influence medical education but medical practice. Throughout all, the importance of the human relationships of medicine is stressed as contrasted with its technology. This humanistic attitude is well summed up in the closing sentence of the book, "It takes a man, not a machine, to understand mankind."

B. S. V.

Atlas of Blood in Children. Kenneth D. Blackfan, M.D., and Louis K. Diamond, M.D. Illustrations by C. Merrill Leister, M.D., New York, 1944, The Commonwealth Fund. Price $12.00.

There have been numerous books on hematology published in the past few years, but few have been devoted to infants and children exclusively. This book fulfils this need and is an important contribution to the pediatrician, general practitioner, and hematologist.

The outstanding feature of the book is the seventy brilliantly executed plates in eight colors from selected fields of blood films stained by Wright's method. The illustrations were done by Doctor Merrill Leister and not only reflect an outstanding artistic ability but are faithful reproductions of what he actually observed under the microscope. This is attested by the plates on leucemic cells which were apparently made from faded slides but are represented just as they were observed. If the atlas is reprinted, these plates should be replaced by illustrations of cells with their normal nuclear pattern and not that due to fading. This is a minor defect and does not mar the otherwise excellent work of this section. Opposite each plate is a line drawing, diagrammatic key permitting the reader to quickly identify the colored representation of the cells. The first few illustrations portray

the developmental cycle of cells of the erythroid, myeloid, lymphoid, monocyte, and thrombocyte series. Then follow patterns of the blood films in normal children at various age periods. The rest of the illustrations are devoted to depicting representative fields of blood films of various pathologic states involving the erythroid and leucopoietic tissues.

Besides this excellent atlas feature which more than justifies the cost of the book, there is a text of 144 pages and a comprehensive bibliography of thirteen pages arranged according to diseases. The text material, although concise, is practical, current, and authoritative. Each disease is briefly discussed from the standpoint of etiology, symptoms, laboratory data, diagnosis, prognosis, and treatment. Occasionally case records are introduced to crystallize the descriptive material. The introductory chapter on the origin and development of blood cells adheres religiously to the polyphyletic theory of Sabin and Doan. However, this material does not blend with the author's use of the neounitarian term "stem cell" to describe those immature cells found in acute leucemias which cannot be positively identified as a myeloblast or lymphoblast. Further, one may question the use of the terminology of "megaloblast" to describe the earliest precursor of the normal red cell series. If the cells pictured on plate 1 are the author's idea of megaloblasts then it is a matter of misuse of the term, for the cells illustrated on plate 1 are unmistakably erythroblasts. The discovery of folic acid and its specific effects in folic acid deficiency anemias in children makes positive identification of megaloblasts of more than academic interest. This should receive consideration in the next reprinting of the atlas, for the book is very outstanding in other respects.

Despite these minor criticisms one can recommend this book as a scholarly contribution to the pediatrician and hematologist. The Commonwealth Fund is deserving of commendation for subsidizing the cost of publication so that it could be made available to the reader at such a low cost. The atlas will undoubtedly be oversubscribed and it is hoped that the authors will make the indicated changes in the second printing.

H. G. P.

Hematology for Students and Practitioners. Willis M. Fowler, A.B., M.D., New York and London, 1945, Paul B. Hoeber, Inc., 449 pages. Price $8.00.

This book on hematology corresponds precisely to its title. It was not written from the viewpoint of academic hematology but from the point of view of an internist interested in presenting as simply and as clearly as possible the practical aspects of the subject. The organization of the text is traditional except for an excellent chapter on transfusion of whole blood and blood derivatives which was written by Dr. Elmer DeGowin. This part of the book is current, comprehensive, and reflects the author's rich background in the subject. It is the feature of the book. The chapter on deficiency anemias is also well done and is a field wherein Doctor Fowler is particularly well qualified to write because of his extensive clinical and experimental work.

The other chapters are well written but are not as current or original in their style of presentation. Some of the information on the so-called "Banti's syndrome," Cooley's anemia, agranulocytosis, Lederer's anemia, and macrocytic anemia are somewhat outdated by reports in current medical literature. The introductory chapters on the hematopoietic system, erythrocytes, leucocytes, thrombocytes and normal hematologic values are concise, clearly presented, and adequate for the readers they were intended to reach. The concluding chapter on hematologic methods is also well organized and sufficient in essential detail for a book of this type.

The bibliography is well selected and ample enough for the material in each chapter except that in some cases significant current references have not been included. The printing on high grade glossy paper is a feature one seldom finds in recent medical books. The illustrations, charts, and diagrams are generous and sharply reproduced in black and white and colors. The colored reproductions of blood cells on the whole are good and those that are not would offend only the hematologist. The microphotographs in black and white are sharp and faithfully portray what one sees in the microscope.

The chapter devoted to hematology in infancy and childhood is inadequate for those specializing in pediatrics and apparently was not intended to meet the needs of this group. The book will also not find much favor with the hematologist or clinical pathologist. Its simplicity of presentation is, however, ideally adapted for the average general practitioner and the medical student beginning his clinical study who desire general orientation in the field of hematology.

H. G. P.

Quarterly Review of Pediatrics. Irving J. Wolman, M.D., Editor-in-Chief, University of Pennsylvania School of Medicine, Vol. 1, No. 1, February, 1946, Washington, D. C.; published by Washington Institute of Medicine.

This is a new type of publication in the field of pediatric literature, similar to those in other fields of medicine by the same publishers which have been available for some time. It is made up of abstracts, summaries, and references to the important new articles selected from national, state, and special journals from this country and abroad, prepared by physicians and others familiar with the special subjects assigned to them. The abstracts are not original articles or reviews as the title might indicate though interpretative or critical comments are given by the editorial staff in judging the pertinence and value of the individual contributions.

Issues will appear quarterly, in February, May, August, and November. The first number includes 122 pages. The abstracts are grouped by subtitles with free cross-references and an index by both subjects and authors. The subject index is unusually well done, indicating all the key words in a title by many cross references. The individual abstracts include the full title of the original article. the author, and reference to the location of publication. Articles in foreign languages include the original language as well as the translation in the title. It is planned that the abstract will be a digest of the articles including especially all the original data. Many of the subsections have at the end a list of references to current articles on that subject. This will enable the reader to know of the articles which have appeared during the quarterly period even though such articles may not have been included as an abstract. Many of the references, however, contain a brief statement of the substance of the article. Particular effort is made to indicate articles containing reviews of the literature on the special subject. The dates on the articles abstracted indicate that prompt publication of the abstract will keep the reader fresh and up to date. This is a most essential feature, for abstracts a year or more old are hardly more than a compilation. It requires a well-organized machinery to have abstracts published promptly and it will tax the quality of the editors and publishers to meet this requirement. The "Bookshelf" or book review department shows a broad coverage of subjects. The reviews are brief and informative rather than critical.

The form of the publication is of high quality. The paper is soft and durable and takes print clearly; the type is well arranged and makes for easy reading. The titles cross the page but the abstract is in double column—again easy reading.

The publishers have chosen a versatile and experienced editorial board with a wide range of interest in all branches of pediatrics. This is a high qualification to meet since pediatrics is a horizontal as well as a vertical specialty which dips into many other fields and specialized areas.

The Quarterly Review of Pediatrics should find an immediate, favorable reception for it fulfills a real need, and it is obvious that the need will be met adequately. It may be pointed out that everyone will find the Review necessary, especially the busy practicing physician. It is a publication to be kept close at hand for quick and frequent reference and will save many a "trip to the library" to dig out a wanted piece of information or "that article I cannot remember exactly."

H. McC.

Pediatric X-ray Diagnosis. John Caffey, A.B., M.D., Associate Professor of Pediatrics, College of Physicians and Surgeons, Columbia University, New York. Cloth, 711 illustrations. Chicago, 1945, Year Book Publishers, Inc., 838 pages. Price $12.50.

This is a highly specialized book about a subject of great pediatric interest and importance. All too often the physician sends the patient to the roentgenologist for study and accepts the latter's interpretation of findings. This implies, among other things, that the physician's knowledge of the situation is not adequately correlated with the x-ray examination and that the x-ray findings are not utilized fully or to the best advantage. The physician must be informed roentgenologically and the roentgenologist must be informed clinically.

The author of the book, by his training, practice, and teaching in the studio, laboratory, clinic, and ward, has emphasized the real necessity of teamwork in roentgenologic studies. His compilation of such a text is the result of this training and has been awaited for a long time. The realization is fully gratifying. This reviewer has examined the book with an inquiring curiosity for errors of omission and commission which search has been fully disappointing. On the other hand, the commendable features are really stimulating.

The paper is of high quality to take the roentgen films fully reproduced. There are full illustrations and diagnoses and the text is brief, concise, well arranged in relation to the illustrations, and fully comprehensive. Both author and publisher may be congratulated on this technical perfection.

The book will be useful to many specialized professional groups, to clinical practitioners, and to the pediatrician. It is a sine qua non for everyday work. It should be on the daily "tool" shelf for constant reference and instruction.

H. McC.

Nutrition and Chemical Growth in Childhood. Volume II, Original Data. Icie G. Macy, Ph.D., Sc.D., Director of the Research Laboratory, Children's Fund of Michigan; with foreword by Laurence Reynolds, M.D., and a supplement by Julia Outhouse Holmes, Ph.D., Springfield, Ill., 1946, Charles C. Thomas, Pages xxv-xlii, 433-1460; Tables 123-597, Figs. 67-773, Cumulative index to Volumes I and II. Price $10.00.

Volume I of this series was published in 1942. It tells of the long-term metabolic studies the author and her colleagues have conducted relating to normal children. As originally planned, Volume II was to deal with the interpretation of the metabolic data. Instead, the current volume is limited in scope to the presentation of the records of thirty-three children who have served as subjects for the studies. A third volume, not yet published, will deal with the analysis and interpretation of the data.

More than one-half of the children were studied recurrently for periods of many months. The records portray the progress of such children, each as a psychobiologic unit, and present in detail the static and progressive values for many physical and physiological constants. The book is profusely illustrated, principally with serial roentgenograms of specific bones and joints. One is impressed by the extensiveness of scope of the observations and the wealth of data relating to each child.

As a book of reference, this volume should serve a useful purpose in many fields of child development. In this regard, it deserves consideration apart from the series as a whole. The value of the data will be enhanced when interpretations are presented in the forthcoming Volume III of the series.

J. D. B.

Diseases of the Nervous System in Infancy, Childhood and Adolescence. Second Edition. Frank R. Ford, M.D., Associate Professor of Neurology, The Johns Hopkins University. Springfield, Ill., 1944, Charles C. Thomas, 1143 pages; 2221 bibliographical references; 164 illustrations; 22 charts; 14 tables. Price $12.50.

The first edition of this book is dated 1937. The second is 1944. Its appearance, however, has been delayed to this date. There are 200 more pages, 468 new bibliographical

references, 40 new illustrations, and 11 new charts in this edition. The book has been rewritten wherever new material could be added or the old improved. The type face is somewhat larger, the page is about the same size, and the paper lighter. The actual amount of new material is considerably increased.

This book is reviewed in its second edition because of its essential usefulness to the the pediatrician and its unique position in this field. The first edition has always occupied an "easy-to-reach" position on this reviewer's bookshelf. As stated in the preface, the author gives his own opinion on most subjects, but where his experience has been limited, he gives the general consensus among leading authorities. It, therefore, carries a personal touch throughout, which increases the interest on the part of the reader. The personal side of the author, however, broadens out to a base which includes many other workers and sources of material at the Johns Hopkins Hospital and Harriet Lane Home. The book can be recommended fully.

H. McC.

Essentials of Pediatrics. Fourth Edition. Philip C. Jeans, A.B., M.D., State University of Iowa; Winifred Rand, A.B., R N., formerly Merrill-Palmer School, Detroit; and Florence G. Blake, R.N., M.A., Yale University School of Nursing. Philadelphia, 1946, J. B. Lippincott Company. 627 pages; 86 illustrations; 9 subjects in color. Price $3.50.

This edition has been revised extensively by rewriting most of the material, and by the addition of new chapters on diseases of the eye, of the blood, and of the glands of internal secretion. The text matter has been reset in double columns with functional running heads. There is still no bibliography. The previous edition is six years old.

Problems of the well-baby clinic are presented concisely in a new chapter, "The Child Health Conference as a Means of Guidance" prepared by Martha B. Webb, R.N., of the Johns Hopkins School of Nursing. A new co-author, Miss Florence G. Blake, has directed the preparation of the material on nursing care.

The pediatrician will find this book useful in his daily work, for there is much in the nursing care that needs his information and attention. For those engaged in teaching, especially for those associated with schools of nursing or who are in charge of nursing services, the new edition will be most welcome. Maybe the next edition will include more in the field of public health nursing service. To nurses, practitioners, and pediatricians alike, this book can be recommended. It should serve as a strengthening bond between the several groups.

H. McC.

Skin Diseases in Children. Second Edition. George M. MacKee, M.D., Professor of Clinical Dermatology and Syphilology, Columbia University, and Anthony C. Cipollaro, M.D., Associate in Dermatology and Syphilology, Columbia University, New York. New York, 1946, Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 448 pages; 225 illustrations. Price $7.50.

This greatly enlarged and rewritten edition with 100 more pages appears after ten years. The first edition has been reprinted in England and a Spanish translation appeared in 1940. New chapters on diseases, important in childhood have been contributed by Dr. Eugene Traub on congenital anomalies, by Dr. Herman Beerman on syphilitic infections, by Dr. Frances Pascher on allergic dermatoses, and by Dr. Nathan Sobel on contagious diseases.

This edition is greatly improved, is rearranged extensively, and includes much new material especially in the field of treatment. This last point is natural since great changes have taken place with the introduction of new chemical therapeutic agents in the past decade. The book is another "must" for every pediatrician and general practitioner. The high standards of printing set in the first edition are preserved.

H. McC.